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HEALTH EFFECTS AND RECOMMENDATIONS FOR ATMOSPHERICAL LEAD, CADMIUM, MERCURY, AND ASBESTOS

Illinois Institute for Environmental Quality

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THIS REPORT GIVES RECOMMENDATIONS FOR AMBIENT AIR QUALITY STANDARDS FOR LEAD, CADMIUM, MERCURY, AND ASBESTOS, BASED ON HUMAN HEALTH CRITERIA. BACKGROUND INFORMATION SUPPORTING THESE RECOMMENDATIONS IS ALSO GIVEN. THE AMBIENT AIR QUALITY STANDARDS RECOMMENDED WERE: 1.5 ug/m^3 FOR LEAD, BASED ON A 24-HOUR AVERAGE SAMPLE THAT IS APPLIED AT ANY GIVEN TIME & AT ANY GIVEN POINT SOURCE; 0.05 ug/m3 FOR CADMIUM, 0.3 ug MERCURY VAPOR/m^3, 1000 ASBESTOS FIBERS/m^3- ALL BASED ON A 24-HOUR AVERAGE SAMPLE.

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Foreword

The Illinois Pollution Control Board asked the Institute for Environmental Quality to conduct studies whose object is to propose air quality standards for pollutants for which no standards now exist.

This publication is an ingredient of the information required to formulate regulations on which the Pollution Control Board can hold public hearings. Other Institute studies, now in progress, will provide supplemental information required to develop regulatory proposals.

This publication deals with atmospheric lead, cadmium, mercury, and asbestos. The Institute's Environmental Health Resource Center has prepared the material based on widespread literature searches, investigations, and critical reviews. Recommendations for further research are made, both as a guide for research agencies, and as evidence of the state-of-the-art with respect to the substance. Additional work is in progress or planned for other substances, including hydrogen sulfide, arsenic, vanadium, manganese, nickel, antimony and chromium.

The Environmental Health Resource Center is a facility of State government established by the Institute for Environmental Quality, and is available to any agency dealing with environmental health problems.

Environmental Health Resource Center
P.O. Box 6998, Chicago, Illinois 60680

Staff

Bertram W. Carnow, M.D. Director
Robert S. Pogrund, Ph. D.
Badi Boulos, M.D., Ph. D.
Richard A. Wadden, Ph. D.
Mark C. Segal, Ph. D.
Ivo Kalacic, M.D., Ph. D.
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The Environmental Health Resource Center is an arm of the Institute for Environmental Quality, managed under contract with the Institute by the University of Illinois School of Public Health at Chicago, Illinois.

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Chapter 1 ATMOSPHERIC LEAD

STANDARD

The ill effects of lead in man are established facts.[1] The atmosphere, along with water and food, are sources of human exposure to this metal. In recognition of the hazards of air-borne lead, the *Environmental Health Resource Center, recommends an ambient air quality standard of 1.5 ug/m^3 based on a 24-hour average sample that is applied at any given time and at any given point source.*

This standard is primarily based upon three human health considerations:

1 Danger to high risk populations, such as children, due to excessive lead body burden;

2 The blood lead level at which metabolic changes take place; and,

3 Human exposure as reflected in epidemiologic data which shows increasing blood lead levels as ambient air lead concentrations increase.

FURTHER RESEARCH

While the recommended standard is regarded by the Center as reasonable, the following research recommendations are suggested for their potential significance in establishing a more adequate informational base to support a lead air quality standard:

1 Determination of single or multiple interactions with other foreign agents or toxic compounds, such as, cadmium, calcium, chromium, bacteria, pesticides, etc.;

2 Investigation of the effect of lead on normal and high risk populations;

3 Epidemiological studies related to appearance of cancer and lead contamination;

4 More pharmacological studies concerning absorption, distribution, and kinetics of lead to determine toxic effects;

5 Toxic manifestations in relation to total lead body burden in the people of Illinois;

6 Placental transfer of lead and its effects on the fetus, in-utero, and new born;

7 Behavioral studies should be conducted on children up to five years old, who have been exposed to prolonged low levels of lead as infants;

8 Studies of the effects of diet and other health factors on lead toxicity.

RATIONALE

The proposed lead standard has been based solely on human health effects. No consideration was given to effects on such things as animals or plants, although inclusion of such information might allow a more stringent standard based upon criteria of more sensitively responding living tissue. Human health effects were reflected in the following three parameters:

1 Total Body Burden for High Risk Populations

Body burden is the amount of a pollutant in the body which produces, or is capable of producing, damage or interference with functions of the body. Intake from air, water,

foods, and cigarettes are some of the sources which contribute to lead body burden. Blood lead level concentration is a variable which is used to characterize lead body burden.

For a child, 40 ug/100 ml of whole blood is considered to be the level above which toxicity and undue body burden occur.[2] Concentrations of lead in blood of children exposed to air with a lead content of about 1 to 3 ug/m^3 varied from 15 to 40 ug/100 ml.[3] However, for a child with anemia, the clinical effect of 40 ug/100 ml, may well be equivalent to that at a higher blood level in a child with normal blood.[2] The observed summer increase of lead levels in children[3a,3b,3c] suggests that a child with blood concentrations on the borderline in winter may well get worse with seasonal change. Children who become acutely ill may mobilize large amounts of lead from bones into the blood stream, with a resulting sharp rise in blood lead concentration. In addition, use of the proposed air standard of 1.5 ug/m^3 indicates that the contribution of inhaled lead to body burden is not unsubstantial and may amount to one-fourth of the total lead absorbed in children.

2 Earliest Adverse Metabolic Effects

In defining a health related standard it is important to consider sub-clinical effects as well as clinical disease. The interference of lead with heme protein synthesis is such a sub-clinical effect. Aminolevulinic acid dehydrase (ALAD) is an important enzyme in heme protein synthesis. It has been found that impaired ALAD activity in red blood cells is the earliest evidence of an adverse metabolic effect due to environmental exposure to increasing concentrations of lead.[4,5] There appears to be no blood lead level threshold below which inhibition of ALAD does not take place.[5] In addition,

ALAD's metabolite (ALA) is excreted in urine when ALAD is inhibited. This effect is initially observable at blood lead levels of 27-35 ug/100 ml and exhibits an increasing exponential relationship above 40 ug/100 ml.[4] It is well to note that the mean value of lead blood levels for groups of males subdivided by occupation and activity has been found to be as high as 38 ug/100 ml, with corresponding annual average air concentrations of 1-3 ug/m^3.[6,7] Given the analogy of diabetes where disease is recognized when glucose spills into the urine, even in the absence of symptoms, it is not unreasonable to consider the condition of ALA in the urine as pre-disease, or at least as a factor which increases body stress. Based on present knowledge, the recommended air quality standard of 1.5 ug/m^3 is considered adequate to prevent the onset of this subclinical effect.

3 Human Exposure

Blood level concentrations from epidemiologic studies of various general and occupational groups have been compared with estimated ambient air exposure to lead. The data suggest that blood lead levels increase as air concentration increases, particularly above 2 ug/m^3.[8] The proposed standards is a recognition of this relationship, and of the prediction that further increases in atmospheric lead will result in higher blood lead levels in the population

ENVIRONMENTAL LEAD SUMMARY

U.S. lead consumption in 1968 was 1,325,000 tons and 140,000 tons was used in Illinois industries.[9,10] Projected increase in the lead industry by the year 2000 is 3.33 million tons or a 1.4% - 3.4% rise annually.[11] Major consumers include gasoline manufacturers, producers of storage batteries, pigments, lead ammunition, solder and metal products.[9] Other atmospheric sources are fly ash from coal combustion, insecticides and non-ferrous foundries.

Annual consumption of lead for use in gasoline additives has increased 65% over the past ten years and has more than quadrupled since 1943.[12] Although only 20% of the lead consumed in 1968 went into petroleum products, almost 99% of the estimated lead emissions into the atmosphere came from gasoline combustion, gasoline transfer, and gasoline antiknock additive manufacture, with over 96% of the emissions coming from gasoline combustion alone (180,000 of 186,614 tons of lead emissions per year).[13]

Man is exposed to lead in the air, water, food and soil. Most lead in the biosphere exists initially in the air since automobile exhaust is the largest single source of emissions. Naturally occuring lead in the atmosphere results from airborne dust, containing on the average 10-15 ug lead/g dust,[14] and from gases diffusing from the earth's crust. The contribution to ambient concentration from these sources has been estimated to be 0.0005 ug/m^3. On the other hand, for the period 1957-1966, urban concentrations of lead ranged from 1 to 3 ug/m^3, and non-urban values from 0.1 - 0.5 ug/m^3,[16,17,18,19] all on an annual average basis. For the period 1967-1969, at least 27 areas, of which Chicago was one, reported maximum quarterly averages in excess of 2 ug/m^3.[20] One Chicago monitoring

station showed a concentration of 2.8 ug/m^3 averaged over the four fall months of 1971.[21]

Concentration of lead in the ambient air is closely correlated with the density of automotive traffic. Thus, concentrations are highest in large cities at sites of heaviest traffic and along highways. The Three City Study[6,7] showed a clear diurnal pattern related to commuter rush hours. Ambient air levels approaching 10 ug/m^3 have occurred within 19 feet of a highway with a traffic volume of 58,000 vehicles per day,[22] while concentrations as high as 25 ug/m^3 have been measured in heavy traffic.[6,7]

Lead exists in the atmosphere primarily in particulate form. Chemically, it may exist as a variety of oxides or as mixed salts, such as PbClBr or $PbNH_2Cl$.[23] However, as a practical matter, ambient measurement and analysis of lead[2] do not usually differentiate between various compound forms. Lead containing particles emitted in automobile exhaust are known to be of submicron size.[24,25] In addition, the mass median diameter of atmospheric particles containing lead has been found to vary from 0.11 to 0.25 microns;[26] and recent measurements in Chicago indicated that over 60% of lead containing particles were smaller than 1 micron in diameter.[26a] The deposition and absorption in the respiratory tract of the lung of particles in this size range varies from 25 to 50%.[27,28]

Lead is removed from the air by gravitational settling of larger particles, coagulation of smaller particles with subsequent settling, collision with trees, buildings, and other surface features, and by association with rain or other forms of precipitation as condensation nuclei or by washout.[29] The lead content of precipitation is strongly associated with the use of lead additives in gasoline. Atmospheric precipitation

samples from 32 U.S. stations showed a positive correlation between the number of gallons of gasoline used and the concentration of lead in the precipitation of each area.[30]

The average lead content of 22 water samples of major rivers of North America was 6.6 ug/liter.[20] The U.S. Public Health Service's prescribed lead standard of 50 ug/liter has not been exceeded since 1962 when continuous monitoring of water supplies began. The natural concentration of lead in soil usually ranges from 2 to 200 ppm exclusive of areas near deposits of lead ore.[20] Soils receive an average of 1 ug/cm^2/year from precipitation and .2 ug/cm^2/year from dustfall.[20] The concentration of lead in atmospheric dustfall and in surface soil of large cities, presumably brought about by emissions from automobiles, can be very high. In Cincinnati at a distance of 25 feet from the roadway, the average lead concentration was 3,397 ug/g of soil, and at 100 feet or more, the average was 2,825 ug/g of soil.[32]

Lead accumulates in humans when the amount absorbed from all sources exceeds the amount that is excreted. Accumulation may continue until age 50 and then appears to level off.[33,34] This build-up is termed the lead body burden and is the amount which produces, or is capable of producing, damage or interference with functions of the body. The blood lead level concentration, usually expressed as ug of lead/100 ml of whole blood, is a variable used to characterize lead body burden.

The major source of lead intake for non-occupationally exposed adults is the diet. Adult oral intake from food and water varies between 100 and 400 ug/day, with 20 ug/day due to water.[3,27] About 5 to 10% of this ingested material is absorbed and retained in the body.[27] As is shown in

the calculation below, the mass of lead inhaled/day is much smaller than that ingested, but the efficiency of retention and absorption is considerably greater (25-50%).[27,28] Assumption of 300 ug/day ingested with 10% absorption, 20m^3/day inhaled with an ambient lead concentration of 1.5 ug/m^3 and 50% absorption, leads to the following estimation:

	Absorbed lead ug/day	%
Adult body burden from diet:	30	67
Adult body burden from air:	15	33
	45	100

Similar calculations using the same absorption factors have correlated reasonably well with lead measurements in feces.[3] It is perhaps instructive to repeat this calculation for children. The inhaled volume is assumed to be 6m^3/day and the diet contribution about one-half that for an adult.[3] The relative contribution due to air in this case is about 25% of the total absorbed. Higher lead air concentrations will, of course, increase this contribution.

Children are a large segment of our population that are peculiarly susceptible to lead. Not only do they breathe a larger volume of air in proportion to their body weight, but their detoxifying enzyme mechanisms have not matured. Exposures through the placental barrier have been reported, which resulted in an increased incidence of birth defects and miscarriages in lead workers.[35,36] Children affected with pica are particularly susceptible to the hazards of lead containing paints. The U.S. Surgeon General has specified that a blood lead concentration of 40 ug/100 ml in children is the level above which toxicity and undue body burden occur.[2] Concentrations of lead in blood of children exposed to air with a lead content of about 1 - 3 ug/m^3 varied from 15 to 40 ug/100 ml.[3] These children were living in dwellings free from hazardous sources of

lead, such as paint and pottery. It is important to note that the clinical effect of 40 ug/100 ml in an anemic child may be equivalent to a higher level in a child with normal blood.[3] Considerable evidence exists that peak occurence of elevated blood lead levels and lead poisoning in children happens in the summer.[3a,3b,3c] Hence, a child with acceptable lead levels in winter may not maintain this condition as the seasons change. And those children who become acutely ill may mobilize other wise relatively inert amounts of lead from bones, with a resultant sharp increase in blood lead levels.

Another factor supporting the blood lead concentration limit of 40 ug/100 ml is the inhibition of the enzyme aminolevulinic acid dehydrase (ALAD). The body's metabolism is mediated by enzyme activity.[1] An enzyme is a biological catalyst, a substance which acts to start up or to stop a process. Enzyme inhibition is a property of lead observed in heme synthesis and cellular electrolyte balance. ALAD is the enzyme which catalyzes the conversion of delta-aminolevulinic acid (ALA) to porphobilinogen, the precursor of heme. There is no well-defined lead blood level below which ALAD inhibition does not take place.[5] In addition, when ALAD inhibition occurs, ALA appears in the urine. This effect is initially observed at blood levels of 27 to 35 ug/100 ml, and, above 40 ug/100 ml, ALA increases exponentially.[4]

There is little documentation concerning the effect of lead on certain "high risk" groups that may be especially sensitive to lead. The sensitivity may be temporary or permanent. Metabolic abnormalities such as glucose-6-phosphate dehydrogenase (G6PD) deficiency and sickle cell disease are examples of permanently altered sensitivity.[13,37,38] Subtle signs of clinical lead poisoning in adults such as fatigue, dizziness, anorexia, and

basophilic stippling have been associated with blood lead levels of about 50 - 80 ug/100 ml and severe lead intoxication is usually thought to occur above 80 ug/100 ml.[1]

Blood level concentrations from epidemiologic studies of various general and occupational groups have been compared with estimated ambient air exposure to lead. The data fit a dose-response relationship reasonably well for ambient exposures above 2 ug/m^3. In addition, laboratory data on experimental subjects exposed to a lead aerosol seemed to agree with the epidemiologic relationship.[8] Although data below 2 ug/m^3 did not disagree with the dose-response correlation, the limited amount of information did not justify strict interpretation. Some of this data also indicated a slight trend towards higher blood lead concentrations in smokers, than in non-smokers,[6,7] possibly due to the 1-2 ug of lead released when a cigarette is burned.[39]

The relationship between lead exposure from the ambient air and blood lead levels is not well defined. As noted above, epidemiologic studies of blood lead levels do suggest a direct correlation with air concentration, and predict that urban residents will indeed have higher blood levels than rural inhabitants.[8] For these studies, estimated air exposure, either occupationally or in the ambient atmosphere, varied from about 1 to 5 ug/m^3. The mean value of blood lead levels for groups of males subdivided by occupation and activity has been found to be as high as 38 ug/100 ml with corresponding annual average air concentrations of 1 - 3 ug/m^3.[6,7] Earlier data, uncorrelated with air pollution, indicated the mean blood level concentration for urban males to be 21 ug/100 ml with a range of 5-59 ug/100 ml.[40] While these values are somewhat lower than 40 ug/100

ml, the range of data, and the existence of susceptible segments of the population, counsel caution in underestimating the present hazards of lead.

Another significant factor is the improvement in lead detection in the past decade. Much of the epidemiologic and laboratory blood lead level data cited were collected in the late 1950's and early 1960's, and were evaluated by fluorimetric techniques.[6,27,40] There is some question whether these methods actually measure all lead present in blood. Hence, a blood lead level of 20 ug/100 ml by fluorimetric techniques may actually be 30 - 40 ug/100 ml.[41] Significantly, the correlation of impaired ALAD activity with blood lead concentration was drawn from atomic absorption data.[4]

Acute and chronic exposure to lead both do harm to the kidney. Cases of an acute nature stemming from a large insult over a relatively short period of time are reversible, but those of a more chronic nature possibly do irreparable harm. At the histologic level, unique intranuclear inclusion bodies have long been considered pathognomonic of severe lead poisoning in man.[42] That protein inclusions in the nuclei of certain cells, including those lining the proximal renal tubules, seem to be a protective device in keeping lead in the nucleus away from vulnerable mitochondria is suggested by the fact that lead poisoned kidney cells consume more oxygen than normal cells.[1]

In acute lead poisoning (80 micrograms/100 ml whole blood or more), kidney dysfunction due to impaired energy metabolism is expressed as Fanconi Syndrome.[43] There is increased loss of aminoacids and phosphate in the urine because of damaged tubular cells which fail to reabsorb these

substances as completely as a normal cell. If phosphate is mobilized from the bones to make up for this insufficiency, stored lead may also be mobilized and cause harm.

Chronic nephritis is a disease characterized by scarring and shrinking of kidney tissue.[44] As a cause of chronic nephritis, lead poisoning is rarely considered in clinical diagnostic study, despite a large body of literature. The best documented evidence for chronic renal disease due to lead is that which relates childhood plubism to the development of lead nephropathy in later life.[45,46,47,48,49,50] Gout is also a consequence of chronic renal injury.[51]

Peripheral neuropathy has been evidenced in occupationally exposed workmen whose blood lead levels were above 70 - 80 ug/100 ml whole blood.[52] The most severe tissue injury was found in the cerebellum or in capillary endothelial cells in the brains of children who died of acute encephalopathy.[53] Among the changes in man associated with higher nervous system function are severe headaches, depression, insomnia, and irritability. Sensory effects include partial or complete blindness, and motor effects from lead intoxication have been described as paralysis, tremors, seizures, and ataxic gait.[54]

At least 25% of those who survive acute encephalopathy from lead poisoning in early childhood have permanent central nervous system injury.[55] The chronic form of lead encephalopathy is usually seen in children over 3 years old who are reported to have developed normally for at least the first 12 to 18 months.[54] It is manifested by a steady loss of acquired skills, speech loss occasionally to the point of mutism, hyperkinetic

and aggresive behavior disorders, and a poorly controlled convulsive disorder.[55] Numerous studies have been conducted on intelligence and motor ability of children after they have been treated for lead encephalopathy or lead intoxication. Many reported some degree of mental impairment caused by lead poisoning.[56,57,58,59,60,61] Impaired motor response was observed in rats exposed to an air concentration of 11 ug/m^3 of lead oxide for 1.5 to 2 months, and impairment increased in severity with increased exposure.[62,63]

Many forms and degrees of liver damage have been described in lead poisoning including fatty infiltration or degeneration, hepatic cell degeneration with nuclear changes, and fibrosis with lobular atrophy. Authors do not agree on the importance and the constancy of the hepatic injuries.[64,65,66,67,68,69,70] The effect of lead on the endocrine and reproductive systems has received relatively little attention, although impairment of thyroid function both in vitro and in vivo in rats and in man has been reported.[71,72]

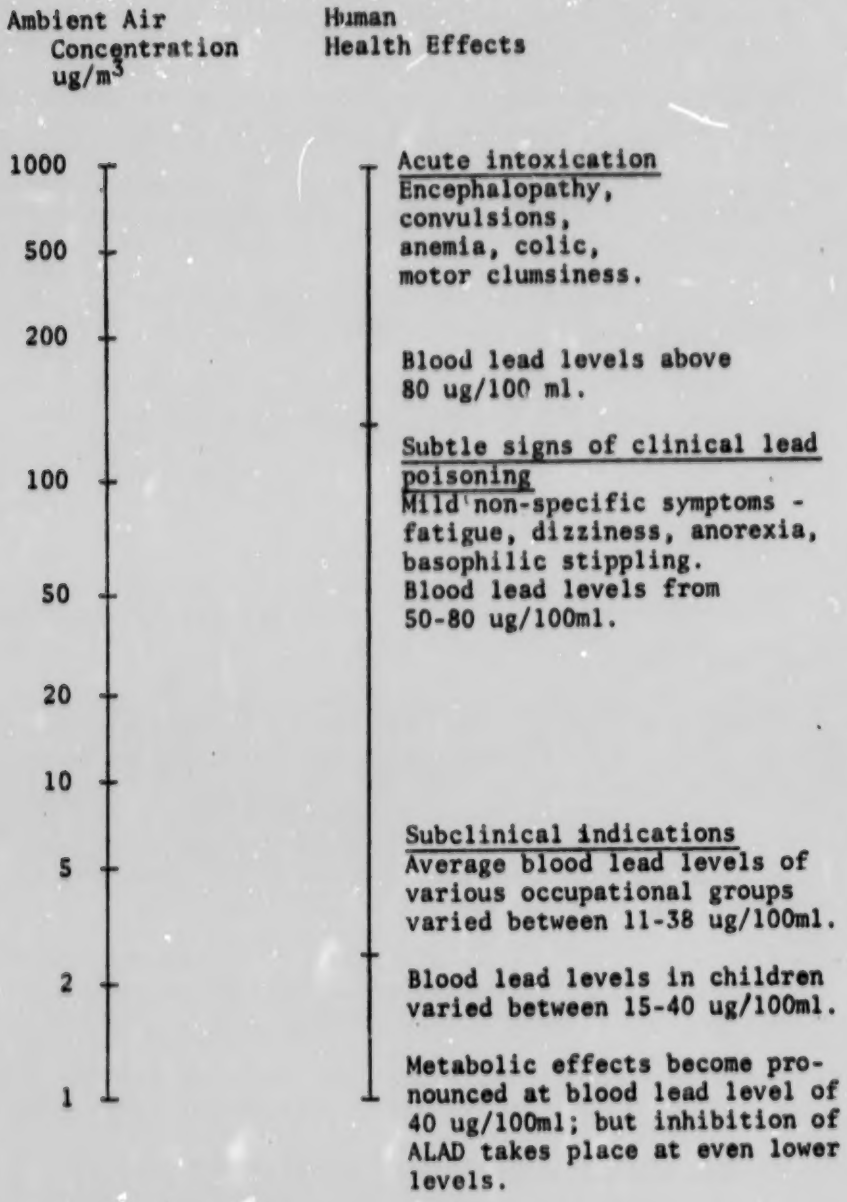
In addition to certain physiological conditions creating a lower tolerance to lead, other agents and substances can increase its effect. There are indications that low dietary calcium or phosphorus, or both, enhance retention of lead in the body. Vitamin D presumably enhances absorption of lead.[74] It has been suggested that the use of alcohol may alter a person's susceptibility to lead poisoning.[75] Decreased longevity has been found in chromium deficient rats with body lead levels comparable to those found in human subjects.[73] Chromium is deficient in the American diet.[76] Lead-treated mice showed greater susceptibility to challenge with Salmonella Typhimurium than controls which received no lead.[77] Lead intoxication in rabbits was accompanied by a reduction in the organism's capacity to produce agglutinins in the course of immunization with E. Typhosa

vaccine.[78] Vitamin C is essential to the production of intercellular connective tissue in the muscles of animals. Lead apparently inhibits the reserve capacity to produce the tissue.[79] The effect of phenobarbital (which induces the production of delta-aminolevulinic acid synthetase and increased heme production) may be beneficial in coping with the deleterious effects of lead intoxication.[80] The repeated demonstration of lead salts inducing renal cancer in rats and the possibility that lead derivatives have caused cancer in man should be further examined.[81,82,83,84] Treatment of pregnant hamsters with various salts of lead resulted in specific skeletal malformations localized within the developing sacral and tail vertebrae.[85] Treatment of chick embryos with lead salts caused hydrocephalus and anterior meningoceles.[86] Chromosomes from leukocyte cultures from mice fed a diet containing 1% lead acetate showed an increased number of gap break abberations.[36] Excessive fetal loss and malformed infants resulting from lead intoxication has been reported in humans and experimental animals.[87]

Figure 1 displays an approximate relationship between human health effects and ambient air exposure.

Figure 1.

Relationship of Human Health Effects
To Air Quality


Ambient Air Concentration ug/m3
Human Health Effects
1000
500
200
100
50
20
10
5
2
1
Acute intoxication
Encephalopathy, convulsions, anemia, colic, motor clumsiness.
Blood lead levels above 80 ug/100 ml.
Subtle signs of clinical lead poisoning
Mild non-specific symptoms - fatigue, dizziness, anorexia, basophilic stippling.
Blood lead levels from 50-80 ug/100ml.
Subclinical indications
Average blood lead levels of various occupational groups varied between 11-38 ug/100ml.
Blood lead levels in children varied between 15-40 ug/100ml.
Metabolic effects become pronounced at blood lead level of 40 ug/100ml; but inhibition of ALAD takes place at even lower levels.

NOTE: Data for Air Quality-Health Effect Relationship primarily taken from references 1,3,4,5,6,7,8 and 27. It is well to mention that references 4, 5, and 27 are studies of industrial exposure (40-45 hours/week), and as such are not directly applicable to the situation of the general population.

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Chapter 2 ATMOSPHERIC CADMIUM

STANDARD

Cadmium is a toxic material present in air, water, food and soil. There is evidence that cadmium stored in the body may accumulate over a period of thirty or forty years[1], that this build up may be associated with shortened life span[2], and that the death rate from heart disease in cities with elevated atmospheric concentrations of cadmium may be higher than in locales where the concentration is low[3,4].

In recognition of these factors, The *Environmental Health Resource Center recommends an ambient air quality standard of 0.05 ug of cadmium/m^3 based on a 24-hour average sample.* This air quality standard, given the present state of knowledge, is considered to be adequate to prevent increase in man's body burden of cadmium, providing there are no drastic increases from other sources, such as food and water.

FURTHER RESEARCH

1 The kinetics of different forms of cadmium on human tissue should be better defined.

2 The synergistic effects with other metals on such kinetics should be evaluated.

3 Pathological manifestations of target organs under influence of cadmium alone, and in combination with other metals, should be correlated with cardio-vascular and neoplastic diseases.

4 The potentiating effect of cadmium in the production of pathological lesions should be evaluated in connection with environmental pollutants, e.g., pesticides, carbon monoxide.

5 The transfer of cadmium across the placental membrane should be measured to determine a dose-response relationship with teratogenic and neoplastic effects.

6 Assessment should be made of the total integrated environmental cadmium stress on general and high risk or enzyme deficient populations.

7 The various chemical forms of cadmium to which man is exposed should be determined and correlated with disease.

RATIONALE

Body burden is the amount of a pollutant in the body which produces, or is capable of producing, damage or interference with functions of the body. The proposed cadmium standard has been based primarily on human health effects. Ambient exposure of other living tissue and the subsequent effects of cadmium have not been evaluated, although use of such information might lead to a more restrictive standard. One of the major hazards of cadmium is that it accumulates in various organs of the body over long periods of time. The presence of this material may well interrupt metabolic activity, particularly in the kidney, and ultimately shorten human life.[1]

Calculation of the proposed air quality standard was based on a cumulative total body burden of 30 mg of cadmium for a 45 year old "standard" man with no known pathology.[1,5] Cigarette smoking is included in the calculation since the contribution from tobacco may amount to 0.01 - 0.08 ug/cigarette.[6,7] Food and water supply about 50 ug/day of which 2.5% is retained.[5] The estimation of the air-borne contribution assumes inhalation of 20 m^3/day and 30% absorption of this material into the body.[5] The calculations are summarized below:

	Cadmium Body Burden Amount Retained		
	ug/day	mg/year	mg/45 years
Food and Water Ingestion: 50 ug/day x 0.025	= 1.25	0.46	20.1
Cigarettes: 0.067 ug/cig. x 10 cig./day	= 0.67	0.25	4.9*
Air: 20 m^3/day x 0.30 x 0.05 ug/m^3	= 0.30	0.11	5.0
			30.0

* Estimate based on 20 year period

Use of 30 mg as a lifetime body burden is not intended to imply that this level is non-toxic. However, until more information becomes available on cadmium toxicity, and providing large increases in intake from other sources do not occur, compliance with the recommended standard should insure that cumulative body burdens greater than 30 mg are not reached.

ENVIRONMENTAL CADMIUM SUMMARY

U.S. cadmium consumption was 13.3 million pounds in 1968 and 15 million pounds in 1969.[8] The greatest use of cadmium is in the electroplating industry followed by plastics, pigments, batteries, and alloys.[9] Over four and a half million pounds of cadmium are emitted into the atmosphere each year in the U.S.[10] The bulk of these emissions are from mining and metallurgical processing and incineration of plated material.

Air pollution from cadmium emissions is mostly in the area around zinc refineries and smelters. The average ambient air concentration of cadmium in urban areas was .025 ug/m^3 in 1966.[11] Data collected for 6 days in the Chicago-Hammond region in 1968 indicated a mean value for all samples of 0.019 ug/m^3 for cadmium with a maximum of 0.08 ug/m^3

and a minimum of less than 0.005 ug/m.[3] Cadmium in water comes from the electroplating industry from electrolytic wastes[8] and, in soft water areas, from cadmium dissolution from zinc galvanized pipes which are contaminated in concentrations of 1% or more.[2] Documentation of cadmium insult on soil yields a varied picture. Not only do fungicides contain zinc and cadmium that apparently are translocated from foliage to fruit, but phosphate fertilizers contain 1.8 ppm cadmium, and superphosphate up to 8.9 ppm.[1,13] Other sources include automobile tires, coal, petroleum,[14,15] and motor oil.

Exposure to cadmium in food varies greatly. Generally seafood, meats and oils have the highest cadmium content with values of .79, .88 and .75 ug/g, respectively. Oysters, crustaceans and mollusks can concentrate the metal 10,000 - 100,000 times from sea water. The practice of refining grains may lead to an increase in the cadmium content of certain grains. One kg of refined flour would supply .38 mg of cadmium, but whole wheat would give only .28 mg. When polished rice is ashed, it has been found to contain 3.5-4 times more cadmium than the unpolished variety.[2,5]

Cadmium has a low order of biological turnover in mammals. It becomes bound to a protein metallothionein in the kidney and accumulates until the fifth or sixth decade, and thereafter diminishes in concentration. Recent evidence suggests that cadmium is carried across the placental barrier.[16] At birth the human infant contains 1 microgram of cadmium. By the time he is 50, the hypothetical standard American man who weighs 154 pounds, has accumulated 30 milligrams of cadmium in his body.[1] By comparison, the standard man in the United Kingdom

has about 15 to 20 milligrams and the Japanese a considerably higher total body burden of as much as 80 milligrams. This latter high accumulation is probably due to large amounts of metal in the rice flour and seafood of the Japanese diet.[17] Of the cadmium in the body, 33% of it is in the kidneys, 14% in the liver and 2% in the lungs. The pancreas contains 0.3% cadmium and the rest is in low concentrations in other tissues.[5] The highest concentration of cadmium in the kidney is found in the cortex.[18]

Daily cadmium intake from food and water has been estimated at 50 ug; approximately 5 ug being excreted into the urine and 43 ug excreted into the feces.[5] This leaves about 2 micrograms absorbed into the system per day. However, recent evidence would suggest that nonsmokers accumulate much less than 1 ug per day,[7] and that the cadmium concentration in cigarette smoke may add 1.5 ug to a person's body burden each day.

Calculation of the proposed air quality standard was based on a cumulative total body burden of 30 mg of cadmium for a 45 year old "standard" man with no known pathology. This approach has been suggested by a number of investigators.[2,5] The contribution from cigarette smoking was estimated on the basis of 20 years exposure and 10 cigarettes/day with 0.067 ug/cigarette[6,7] retained in the body. About 2.5% of ingested cadmium was assumed to be retained, and about 30% of that which was inhaled.[5] The daily inhaled volume of air was taken as $20 m^3$/day. The total body burden calculation is as follows:

		Cadmium Body Burden Amount Retained		
		ug/day	mg/year	mg/45 years
Food and Water Ingestion: 50 ug/day x 0.025	=	1.25	0.46	20.1
Cigarettes: 0.067 ug/cig. x 10 cig./day	=	0.67	0.25	4.9*
Air: $20m^3$ day x 0.30 x 0.05 ug/m^3	=	0.30	0.11	5.0
				30.0

* Estimate based on 20 year period.

Since so little is known about the long term effects of cadmium, choice of 30 mg as a lifetime body burden is not intended to imply that this level is non-toxic. However, until more information becomes available on cadmium toxicity, and providing large increases in intake from other sources do not occur, compliance with the recommended standard should insure that cumulative body burdens greater than 30 mg are not reached.

Assessment of cadmium intake and body burden is important for three reasons: 1) It has been shown that persons 80 years of age average only about half as much cadmium in their kidneys as persons 45 years old.[2] The possibility exists that large concentrations of cadmium in the body, coupled with a high ratio of cadmium to zinc, shorten one's life. This interpretation is supported by studies that show increased mortality and shortened life span in rats fed cadmium. Other theories may also explain this phenomenon, e.g., excretion of cadmium may increase and absorption decrease with age, or the fact that industrial consumption of cadmium has been increasing since 1930.[5] Nonetheless, the effect of cadmium intake on life span should not be overlooked. 2) Whereas zinc is a normal body constituent entering into co-factor activity in several

enzyme systems, cadmium appears to be non-essential though associated with zinc in the geosphere and biosphere. The kidneys have little or no cadmium at birth but in an adult, the cadmium to zinc ratio may rise to 60%. Such high renal ratios have been associated with a higher incidence of death from arterial hypertension.[5] Because cadmium in human kidney is bound by metallothionein which also contains zinc and because cadmium, competes with zinc on the same binding sites (presumably thiol groups), experimenters are interested in the relative amounts of each metal. In small mammals, cadmium replaces zinc but zinc will not replace cadmium which suggests that cadmium is more firmly bound. Cadmium is therefore believed to act as an antimetabolite for zinc in some systems. 3) Intake and body burden may be correlated with possible disease states, such as hypertension, cancer, and kidney disease.[3,4,5]

The metabolism of cadmium is intimately connected with zinc metabolism.[1,19,20] In addition to metallothionein binding cadmium to the kidney, the binding potential of this protein has been associated with cadmium levels in the liver, blood and duodenum.[21] As cadmium concentrations in blood during exposure will vary independently of renal concentration, the determination of cadmium in blood is of limited assistance for making an estimate of renal concentrations.[22] Normal concentrations of cadmium in blood will be well below 1 ug/100 ml whole blood.[23] The cadmium in blood concentrations for exposed workers varies between 1 and 10 ug/100 ml whole blood.[5]

Cadmium has a particular affinity for sulfhydryl groups and also, to a certain extent, for hydroxyl groups and ligands containing nitrogen.[24] The inhibitory action of cadmium on enzymes is in most cases due to a

binding to essential SH groups.[24] It is lethal to various forms of aquatic life at low concentrations, such as sticklebacks at .2 ppm, goldfish at .17 ppm and the flatworm at 2.6 ppm.[5]

Workers with prolonged exposure to cadmium oxide dust (at concentrations as low as 100 micrograms/m^3 for a year) developed renal tubular dysfunction.[25,26,27] A characteristic sign of this renal dysfunction is proteinuria. This is considered to be due to a decreased tubular reabsorption of filtered proteins. Other such signs usually appearing after the proteinuria are glycosuria and aminoaciduria and changes in the metabolism of calcium and phosphorus. Evidence from animal experiments and from analyses of cadmium in kidneys from workers exposed to cadmium indicates that this dysfunction becomes manifest at levels around 200 ppm cadmium (wet weight) in the renal cortex.[27,28]

Results of investigations thus far do not support a hypothesis that cadmium is causally related to cardiovascular disease in man. However, there are reasons to study this question further. Animal studies suggest that such a relationship is not unreasonable.[29,30,31] Epidemiological studies on human beings have indicated that patients with hypertension have increased cadmium levels in their renal tissue,[31,32] and that there is a marked correlation between death rates from hypertension and arteriosclerotic heart disease, and air concentrations of cadmium.[3,4] This latter relationship, however, is still undergoing evaluation.[33] Another role that cadmium may fulfill is as a contributory factor in an individual whose hypertensive pattern has already been set since childhood.[34]

Anemia and osteomalacia are two other well documented health effects of chronic cadmium exposure.[22,35,36,37] Cadmium exposure damages the olfactory nerve

often resulting in anosmia.[35,38] As with lung and kidney damage, duration of exposure is critical. Animal experiments demonstrated that cerebellar damage occurred, which was associated with cadmium treatment during the first few days of life, but that older animals became less susceptible.[39,40,41]

Several studies have reported on the prevalence of cancer among workers exposed to cadmium oxide dust in the production of alkaline batteries.[28,35,38] However, most of the data on cadmium's tumor production capabilities come from animals injected subcutaneously or intramuscularly with cadmium compounds.[42,43] Synteratogenic effects of cadmium have been demonstrated in pregnant hamsters.[44,45]

Cases of chronic cadmium poisoning in industry resulting in emphysema have been heavily documented. Autopsies performed on 60 patients chosen at random, who had died from a variety of causes, showed the cadmium liver content of those dying from emphysema to be three times higher than that of the other subjects.[46,47]

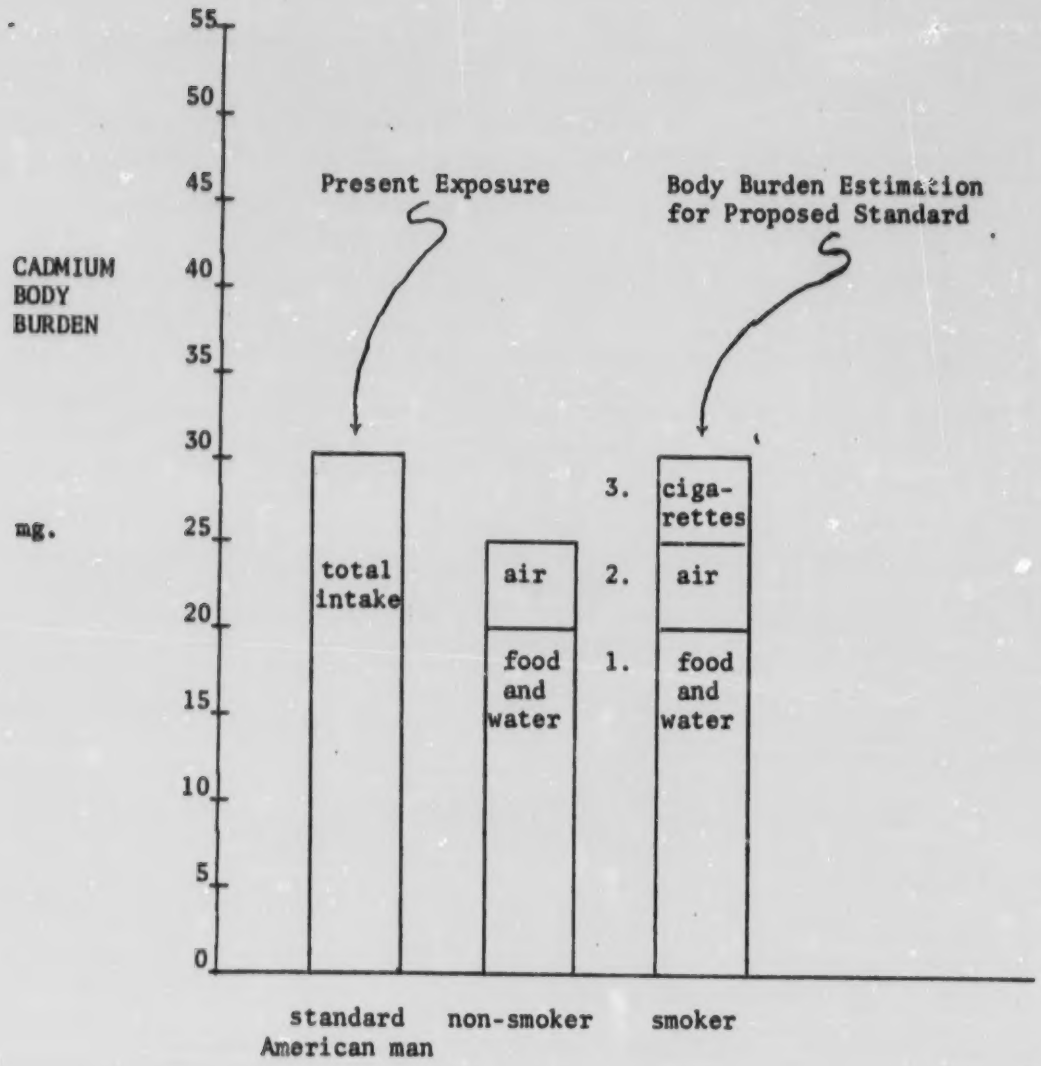
Table I presents some of the known dose-response information regarding cadmium. Figure I shows the relative contribution of several sources to total body burden.

Table 1
Cadmium Dose-Response Relationships

KIDNEY DYSFUNCTION	CONCENTRATION AND SOURCE	DURATION OF EXPOSURE	COMMENTS	REFERENCE
Proteinuria	200-15,000 ug/m^3 (air)	5-7 years	alkaline battery industry--Sweden.	Friberg, L., Arch. Ind. Hyg. Occu. Med. 1:458, 1950.
Proteinuria (44 percent of study)	100 ug/m^3-236,000 ug/m^3 (air)	10 year period	cadmium oxide dust; industrial workers.	Potts, Ann. Occu. Hyg. 8:55, 1965
Slight proteinuria and anemia	130 ug/m^3(air)	one year	average exposure at nose level in smelting works; no loss of smell or symptoms.	Tauchiya, Arch. Environ. Health, 14:875, 1967.
CIRCULATORY				
Hypertension, arteriosclerosis, etc.	.000-.062 ug/m^3 (Cadmium in air of 28 cities)	based on annual average	correlation coef. (r=.76) between cadmium concentration and diseases of the heart.	Carroll, J.A.M.A. 198: 267, 1966.
Hypertension	5 ug/ml (water)	one year	in experimental rats	Schroeder, Circulation, 35:570, 1967.
Hypertension	(water)		humans-softness of H_2O and heart disease correlate.	Schroeder, J. Chron. Dis. 18:647, 1965.
RESPIRATORY				
Emphysema and Proteinuria	did not exceed an average of 270 ug/m^3 (air)	up to 15 years	men casting copper-cadmium alloys; 100 men studied, 16 with emphysema.	Bonnell, J., Brit. J. Ind. Med., 12:181, 1955.
Bronchitis and Emphysema	all sources	lifetime	Livers of 60 patients examined for cadmium; mean cadmium level in liver 3 times higher in those who had died from emphysema as in other patients.	Lewis, G., et al, Lancet, 2:1330, 1969.

Figure I

CONTRIBUTION OF VARIOUS SOURCES TO
CADMIUM BODY BURDEN OF MAN AT AGE 45



1. based on 1.25 ug cadmium uptake for food and water per day

2. based on 0.3 ug cadmium per day uptake from air (0.05 ug/m^3)

3. based on 0.67 ug cadmium uptake from cigarettes per day

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Chapter 3 ATMOSPHERIC MERCURY

STANDARD

Man's extraction and consumption of mercury and its compounds have contributed to the pollution of our air, water, food, and soil. Available evidence indicates that long term exposure to low concentrations of atmospheric mercury may lead to psychological disturbances and deleterious effects to the central nervous system.[1,2,3]

The *Environmental Health Resource Center recommends an ambient air quality standard of 0.3 ug mercury vapor/m^3 based on a 24-hour average sample.* This standard is based on evidence which suggests that a certain dietary intake of methylmercury leads to health effects similar to those suffered following occupational inhalation exposure to an equivalent amount of mercury vapor.[4] This standard will also apply to mercury in the particulate form.

FURTHER RESEARCH

There are gaps in knowledge in nearly all aspects of the problem of environmental mercury contamination. Further research is recommended in the following areas:

1 Quantitative and qualitative determination of the chemical and physical forms of mercury in the air both near to and remote from known sources and the transformation they undergo.

2 Development of improved analytic methods to distinguish and measure the various organic and inorganic mercury compounds which

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may exist in the environment. Improved methods for the determination of very small concentrations of mercury.

3 Better determination of the absorption, distribution and excretion of mercury compounds in man.

4 Determination of the site and mode of cellular action, whether cell damage can occur from a low level chronic exposure to mercury, and whether this exposure can be expressed clinically or subclinically.

5 Studies to determine genetic and congenital effects:

a Experiments on animals should be performed to determine maternal-fetal effects including possible genetic abnormalities chromosomal aberrations and teratogenic effects in relation to long and short term exposure at various levels.

b Follow-up studies should be conducted to observe neurologic damage or behavioral dysfunction. Pathologic findings should be correlated carefully with exposures and tissue levels of mercury.

c The possible consequences of the transmission of mercury through milk should be investigated.

6 Determination of a biochemical measurement whose deviation from normal regularly precedes development of toxic effects.

7 Body burden studies should be carried out:

a This would include total diet studies involving sampling of tissues of pork, veal and fish, of baby food, etc. Pregnant women in obstetrical clinics should be interviewed to obtain information on nutrition for correlation of food intakes with maternal and newborn blood mercury levels.

b Information on consumption of fish should be gathered so that population subgroups likely to have had higher than usual dietary intakes can be identified. Frequency distribution patterns of fish ingestion should be correlated with known levels of mercury and other neurotoxic chemical residues in fish in order to relate to possible neurologic responses in man.

c The contribution to intake of mercury from other sources such as air, water, and medicinal applications should be determined.

8 Better guidelines of tissue change and mercury levels in accesible tissues such as hair, blood, and skin should be developed.

9 Clinical screening tests should be conducted in which comprehensive physical and psychological examinations and laboratory procedures are performed with particular attention to the early detection of clinical and subclinical reaction.

10 Experimental examination of possible synergisms of mercury with other neurotoxic chemicals (pesticides, PCB's, lead, etc.), should be undertaken.

RATIONALE

Mercury may exist in the atmosphere as vapor or aerosol in inorganic or organic form.[5] Atmospheric emissions from industrial sources are believed to be emitted as elemental mercury vapor or aerosol.[5] It has been stated that most mercury compounds degrade to mercury metal under the action of sunlight.[6] Recent measurements in Chicago[7] and at 4 industrial and 2 residential sampling sites[8] in the State of Illinois indicate that

concentrations of mercury vapor are much greater than concentrations of particulate.

Human volunteer studies have shown that following inhalation of metallic mercury vapor, absorption is rapid and nearly complete (80%).[9] The extent of absorption of aerosols of mercury salts in the respiratory tract is believed to be less than that of the vapor.[10] The percent of absorption of vapors of mercury organic compounds is also unknown,[10] but their physical properties suggest it should be high. When inhaled as aerosols, these compounds are likely to dissolve quickly in body fluids.

A rationale for an air standard for any pollutant requires consideration of total intake of that substance from all possible sources. Although airborne mercury seems to be largely a localized problem at various industries, power plants, incinerators and mercury mines and smelters, it is an additional insult to the ecosystem since it may eventually reach the soil or water. Furthermore, the effect on the general population, and possibly the fetus, living in the vicinity of point sources may be significant.

The Environmental Health Resource Center recommends an ambient air quality standard of 0.3 ug of mercury/m^3. A daily intake of 30 ug/day is considered to be safe.[4] Studies suggest that the average dietary intake in the U.S. is 25 ug/day.[11] This allows for inhalation of 5 ug/day. Since adults breathe 20 m^3 of air per day and since 80% of the inhaled mercury is absorbed,[9] a standard of 0.3 ug/m^3 is necessary in order to assure inhalation of not more than 5 ug/day.

ENVIRONMENTAL MERCURY SUMMARY

Forms of Mercury: Mercury may exist in the environment in many chemical and physical forms. In the elemental state it is a silvery liquid with the highest vapor pressure of all metals. However, very little mercury exists in its natural state. It reacts with a great variety of inorganic substances to form such compounds as mercurous or mercuric salts. Mercury may also bond with organic compounds to form, for example, alkyl mercury compounds, such as methyl or diethyl mercury, or aryl mercury compounds such as phenyl mercury.

Mercury and its compounds may exist as vapor or as an aerosol. An aerosol or dust is formed as the result of the dispersion of a solid or liquid in the air. In the water environment, mercury may solubilize or complex with other compounds.

All these forms are subject to transformation both in the environment and the human body. The toxicity of the mercury depends on the form in which it exists. Much is still unknown about the transport of these various forms throughout the environment.

Sources: The natural background level of mercury is due to its occurrence in minerals and rocks. The mercury from these natural sources may vaporize, elevating atmospheric levels. This atmospheric mercury may be washed by rain to the soil. Here it may evaporate or reach streams or groundwater.

Man's extraction and consumption of mercury compounds have contributed to the problem of mercury pollution. Mining, smelting, and refining operations release tons of mercury into the atmosphere each year.[12] Consumption in 1969 was 79,104 flasks (1 flask = 76 lbs.).[13] Consumers of

mercury and therefore potential polluters include the following industries: chlor-alkali, agricultural, electrical apparatus, paper and pulp, paint, instrument, chemical and metallurgical, medical and dental laboratories. Since mid-1970, the consumption of mercury in chlor-alkali plants, agriculture, and paper industries has been reduced.[4] Total use has decreased by more than one-third of consumption for the same period in 1969. The largest source of mercury pollution may be from the burning of coal by power plants.[14] Mercury in burning coal is vaporized and released into the atmosphere.[15] Municipal incinerators also contribute mercury to the air. Even if restrictions are placed on the contributing industries, power plants, and incinerators and the quantity of mercury released into the environment is reduced, the problem of mercury pollution will not be immediately resolved. Because inorganic mercury is converted to methylmercury in the sediment, lakes already contaminated by inorganic mercury will provide a continuous source for methylmercury production. This mercury may persist in the environment for an estimated 100 years.[12,16]

Levels in the Environment: Atmospheric concentrations of mercury over land sources are a function of certain meteorological conditions such as temperature, barometric pressure, and rainfall.[17,18] Concentrations are highest over mineral deposits, but mercury has also been detected over unmineralized areas.[19] Concentrations in particulate and vapor form have been measured in various cities and range from 1 to 210 ug/m^3.[2,7,3,20,21,22] Recent measurements in Chicago of mercury in suspended particulate matter and mercury vapor revealed average levels of 3.6 ng/m^3 and 175 ng/m^3, respectively.[7] Concentrations emitted from stacks of power plants, incinerators, and certain industries in Illinois and Missouri have been determined.[15,23]

The State of Illinois Institute for Environmental Quality has sampled at 4 industrial and 2 residential sites in the State.[8]

Mercury is conveyed to the water environment either directly from the atmosphere, or as rainwater, in run-off, through groundwater, or in industrial or municipal waste. Low levels have been found in most U.S. rivers (65% contained less than 0.1 ppb).[24] Because mercury tends to accumulate in bottom sediments, concentrations in such sediments are often higher than in water.[25,26] Mercury has also been found in soil,[20,27,28] plants and and sludge (0.8 to 120 ppm).[19,29,30,31,32,33] The presence of low levels of mercury have been found in most foods (3-1000 ppb) except fish,[5,34] which have been found to contain up to 40 ppm in mercury-polluted waters[25,35,36] in Japan. Coal contains trace amounts of mercury which, when burned, is volatilized and released.[37,38,39] Concentrations in U.S. coal range from 0.012 to 33 ppm. Illinois coal contains 0.04 to 0.49 ppm with an average of 0.18 ppm.[40]

Absorption: The absorption of any mercury compound depends on its physicochemical properties such as its solubility, molecular size, and its ionic state.

Because of its low water solubility, mercury vapor is only slightly dissolved in the fluids and mucous membranes of the upper respiratory tract.[41] It achieves passage to the lower respiratory tract and reaches the alveoli. Experiments in guinea pigs, dogs and rats have shown that between 25% and 100% of mercury vapor is absorbed.[41,42,43,44] Any mercury which is retained in the lungs is either exhaled or later absorbed by the blood. Human volunteer studies have shown 67% to 88% alveolar absorption.[9] Alcohol consumption was shown to reduce mercury absorption in the blood.[45]

The amount and rate of absorption of aerosols of mercury salts in the respiratory tract has not been well established and depends on the previously mentioned physicochemical properties.[10] It is likely that respiratory absorption of aerosols of inorganic mercury is less than that of mercury vapor.[46]

Little information regarding the uptake and absorption of inhaled vapors or dusts of organic mercury compounds exists.[10] However, there is a definite possibility of exposure to, and pulmonary absorption of, organic mercury compounds since they too are volatile. The rate of absorption of vapors of organic mercury compounds by the respiratory tract is not known, but their physical properties indicate high efficiency. In aerosol form, following inhalation, such compounds are likely to dissolve rapidly in body fluids and to be distributed to the blood.[10]

Organic mercury compounds are much more readily absorbed than inorganic mercury salts following their ingestion. Up to 25% of inorganic mercury ingested is subject to gastrointestinal uptake in rats or mice.[47] However, after 2 days of exposure of mice to mercuric chloride, absorption may be less than 2% of the daily intake.[47] Both animal and human volunteer experiments indicate that gastrointestinal absorption of methylmercury is 90-100%.[47,48,49] Absorption of phenyl mercury in rats is 50-80%.[50]

Biotransformation: Evidence indicates that mercury, which may exist as the elemental metal, as a mercurous or mercuric salt, or as an organomercury compound, undergoes biotransformation in the body. Such biotransformation is an important factor in determining the toxicity of the compound, since the biochemical effect depends in part on the oxidation state of mercury and whether or not it exists in the inorganic or organic form.[51]

Oxidation of elemental mercury vapor to mercuric ion occurs in the blood, chiefly in the erythrocytes, as well as in the tissues.[51] It is known that the more readily diffusible vapor may accumulate in the brain, reaching levels 10 times greater than those following exposure to mercuric chloride.[52] This uptake by the brain may be due to the transient existence of unchanged vapor in the blood which finds its way to the brain in a short period of time.[52] It has also been found that mercuric ion can be converted to mercury vapor to some extent.[53]

Experiments have shown that phenyl mercury is absorbed and transported unchanged in the blood, but biotransformation to inorganic mercury occurs in the liver and kidney.[54,55]

Biotransformation of organic mercury compounds is believed to result from cleavage of the carbon mercury bond.[55,56] Methylmercury accumulates in all tissues, especially the red blood cells and the brain and is then very slowly converted to inorganic mercury.[55] This conversion occurs chiefly in the kidney and liver.[56,57]

Distribution of Mercury Compounds: Mercury in plasma is bound to plasma proteins, whereas in the red blood cells, it is bound to hemoglobin.[41] After exposure of rats, squirrel monkeys, and rabbits to mercury vapor, 67% to 87% of the mercury was bound to the red cells, whereas, following injection with a mercuric salt, 25% of the total blood level was in the red blood cells. Aryl mercury is approximately evenly distributed between plasma and red cells. Ninety percent of methylmercury is bound to red cells, but the fraction in plasma varies among species.[49] Concentrations in human fetal red blood cells were greater than in maternal red blood cells, whereas concentrations in plasma were less.[59,60]

Following acute exposure to inorganic mercury salts, highest concentrations of mercury have been found in the kidney and second highest in the liver.[10] Varying concentrations have also been found in the brain, thyroid, spleen, pituitary, pancreas, intestine, muscle, heart, testes, bone, fat, and skin as well as the blood and lungs.[10,61] Blood levels are high immediately after exposure but diminish rapidly with time.

The distribution pattern depends on the mode of administration, dose and species. Considerable differences exist among the organs in the rates of uptake, retention, and elimination of mercury compounds.[61]

Except for the greater uptake by the brain and the transient deposition of mercury vapor in the lungs, the distribution and retention of the inhaled vapor is similar to that of the same amount of injected mercuric mercury.[43,58] Distribution is not influenced by exposure level.[62]

There are considerable differences in distribution patterns of methylmercury among the different mammalian species studied. Some studies suggest that levels are usually highest in the liver and kidney, whereas others have found uniform distribution. Levels in the central nervous system are usually lower than in these organs but much higher when compared to levels following exposure to inorganic mercury.[63] Accumulation of mercury in the brain is slow, but it is retained there longer than in other organs.[64] One study showed that nearly all mercury in rat brain tissue was in the form of methylmercury,[65] whereas human autopsy studies revealed no detectable methylmercury in the brain.[66] Human tracer studies with methylmercury have shown that 50% of the activity in the body was localized in the liver and 10% in the head.[48]

Distribution of phenyl mercury is dose-related. Initially distribution is similar to that following administration of short chain alkyl

mercury compounds, but later approaches a distribution pattern like that of inorganic mercury.[61] This is probably due to biotransformation to inorganic mercury in the liver and kidney. Levels in the CNS are comparable to those of mercury salts.

Retention and Excretion: Whole-body retention and elimination of inorganic mercury depend on its biological half-life.[68] One study showed a 3 phase clearance of mercuric nitrate in rats - a rapid phase with 35% clearance in a few days, a second phase in which 50% cleared with a half-time of 30 days, and a third phase in which 15% required 100 days for clearance.[69,70] Other species have shown different patterns. Human tracer studies of whole-body retention revealed fecal excretion of 85% of the ingested mercury in 4 to 5 days.[71] The remaining 15% had a half-life of about 42 days.[71]

> Although biological half-life of mercury in the whole body gives a general idea about the kinetics of mercury turnover, it is the biological half-life in critical organs that is of importance for the accumulation and risk of intoxication at repeated exposure. The change of distribution pattern with time after a single injection of mercuric mercury reflects the varying rates of elimination from different parts of the body. Organs which have uptake and retention conditions favoring a high accumulation of mercury at a particular exposure are the same organs which are critical at that kind of exposure. Thus at acute exposure or even at prolonged exposure to mercuric mercury, the kidney invariably contains the highest concentrations of mercury, but at prolonged exposure certain parts of the brain also are apt to reach high concentration levels.[71]

Mercuric mercury is excreted chiefly in urine and feces but may also be found in milk, sweat, saliva, and hair.[10,71] The route of elimination depends on dose and route of administration.[71]

Elemental mercury vapor follows a pattern of retention and elimination similar to that of mercuric mercury except for its greater

accumulation and retention in the brain and the transient retention of mercury vapor in the lung.[68] It is unclear whether or not the excretion pattern of mercury vapor is like that of mercuric mercury.

Methylmercury is nearly completely absorbed from the intestine and is excreted at a slower rate from the body than all other forms of mercury.[47,48,49] The extreme toxicity of methylmercury may be related to its slow excretion and accumulation in the brain. The slow excretion may be due to the trapping of methylmercury by the red blood cells and its slow metabolism to inorganic mercury.[65]

Excretion of methylmercury is largely via the fecal route, but mercury has also been found in the urine, hair, and milk.[72] Up to 13% in urine and 50% in feces has been in the inorganic form.[65]

A human tracer study with methylmercury revealed a half-life for the mercury localized in the head to be about 85 days.[48] The whole-body biological half-life was 70-74 days. One percent of the body burden is excreted per day.[73] Another study showed a biological half-life of 69-70 days in red blood cells and 78-83 days in the plasma. Assuming a half-life for humans of about 69 days, steady state level would then be reached in about one year.[74]

Mercury Level in Normal and Exposed Humans: Autopsy studies of mercury levels in the tissues of normal and exposed humans show considerable variation, but highest levels have been most frequently found in kidney and liver.[75,76,77,78] A recent study suggests, however, that no specific organ accumulates more mercury than all others.[66] One study reports no mercury accumulation with age while another noted a biphasic curve of

tissue levels throughout an individual's lifetime. Peaks occurred in early childhood and middle age. This study also observed a sharp drop in total mercury content of most human organs during the last 60 years. The upper limit for "normal" mercury levels in urine is 20 to 25 ug/l and in blood, 4 to 5 ug/100 ml.[79] Seventy-five percent of the normal population have less than .5 ug/100 ml. of blood, while 95% have less than 4 ug/100 ml.[47] Most of the recent work involving the determination of mercury levels in humans has been conducted in Scandinavia and Japan where high concentrations of methylmercury have been found in fish and where fish consumption is frequent. Levels in urine, blood and hair vary with exposure.[59,60,80,81]

Estimation of Body Burden: Mercury accumulates in humans when the amount absorbed from all sources exceeds the amount that is excreted. This build-up is termed the mercury body burden and is the amount which produces, or is capable of producing, damage or interference with functions of the body. Although the fraction of ingested mercury absorbed depends somewhat on the chemical form,[47,48,49] estimates have been made of the various contributions to mercury body burden.[4] Assumption of 25 ug/day in the diet of which 100% is retained,[11,47,48,49] and a contribution of 5 ug/day from inhalation based on $20m^3$/day, 0.3 ug/m^3 and 80% absorption,[9] results in retention of 30 ug/day. This level of retention has been suggested as one which is acceptable based on the present state of knowledge of the effects of mercury.[4]

Effects of Mercury Poisoning: Clinical Manifestations of Metallic and Iorganic Mercury Poisoning: Inhalation of high concentrations of mercury vapor or inorganic dusts or the ingestion of mercuric salts may

result in acute mercury poisoning. Such incidents are infrequent but may result from occupational exposure or medicinal overdose. Acute cases of vapor poisoning have occurred following exposure to 1.2 to 8.5 mg of mercury/m^3 and usually result primarily in digestive and renal disturbances.[3] The symptoms include a metallic taste, nausea, abdominal pain, vomiting, diarrhea, headache, anuria and uremia, and albuminuria. This is followed by gingivitis, stomatitis, increased salivation, loosening of teeth, and ulceration of the lips and cheeks.[3,82] Severe exposure to mercury vapor may produce pulmonary irritation such as tightness, chest pains, difficulty in breathing, and coughing.[83] Recovery may occur in 10 to 14 days in mild poisoning cases, but development of chronic symptoms is possible.[3]

Mercury vapor is the most common source of chronic occupational exposure. When exposure to inorganic dusts occurs, it is usually in combination with exposure to vapor. A syndrome referred to as micromercurialism which results from long term exposure to low concentrations of atmospheric mercury is characterized by more mild symptoms than those of classical mercurialism.[1] These include decreased productivity, increased fatigue and nervous irritability, loss of memory, loss of self confidence and later the more severe problems associated with classical mercurialism.[1] Classical mercurialism involves deleterious effects to the central nervous system which include tremors of the hands, head, lips, tongue or jaw, and psychological disturbances, such as erethism (characterized by undue embarrassment, timidity, depression, discouragement, irritability, resentfulness or excitability).[3] These may be followed by ataxia in the form of dysarthria (stammering) or dysphagia (difficulty in swallowing) and later coordination difficulties in the extremities.[2] Some symptoms are similar to those of acute exposure. Mercurialentis, a hazy appearance

of the anterior lens, may also appear.

Clinical Manifestations of Organic Mercury Poisoning: On inhalation of alkyl mercury compounds, the mucous membranes of the nose, mouth, and throat become irritated after short exposure. The symptoms usually disappear after termination of exposure. The symptoms of alkyl mercury poisoning have been observed following occupational exposure and in mass outbreaks and have been induced in experimental animals.[34,80,86-98]

The symptoms of methylmercury poisoning which are similar following acute and chronic exposures, are neurological and include:

1 Numbness and tingling of lips, tongue and extremities
2 Concentric constriction of the visual fields which might progress to blindness.
3 Impairment of hearing
4 Ataxia of gait
5 Reflex changes, including extensor plantar response
6 Dysphagia (difficulty in swallowing)
7 Dysarthria (inability to speak clearly)
8 Intellectual deterioration
9 Cerebral palsy-like disease in children born to exposed mothers

A latent period of 1 to 2 months following exposure to methylmercury occurs before symptoms are manifested. The severity of symptoms depends on the extent of exposure. In light poisoning cases several symptoms may be absent and partial recovery may take place. However, when intoxication is severe, symptoms are irreversible.[80]

Symptoms of ethylmercury poisoning are similar to those for methylmercury with a few exceptions. Motor weakness of the extremities with progressive muscular atrophy and widespread fasciculations, changes in the

electrocardiogram, as well as gastrointestional disturbances have been reported.[104] Symptoms following exposure to methoxyethyl and phenyl mercury are similar to those following exposure to inorganic mercury and are probably due to such compounds.[10]

Cellular Mode of Action: The ultimate effect of mercury and its compounds is believed to be the inhibition of enzymes.[100,101,102] Hughes has suggested[103] that the principal reaction of all mercury compounds is with the sulfhydryl groups with which they form mercury mercaptide, and that the variations in distribution and effects are dependent on this reaction. This affinity results in the association of mercury compounds with human blood plasma as well as red cells which contain 60 times as much sulfhydryl in their hemoglobin as plasma.

In addition to its affinity for thiol groups, mercury has an affinity for organic ligands such as amino-, carbonyl-, and hydroxyl- substituents which are often part of enzyme systems. In vitro experiments have demonstrated the inhibition by mercury of such enzymes as pyridine nucleotide and flavin enzymes, other redox enzymes, hydrolytic and transferring enzymes. Inhibited enzyme systems also include phenolsulfate conjugation, citrulline phosphorolysis, oxidative mitochondrial and serine biosynthesis. In addition to enzyme inhibition, mercury produces potassium ion loss, blocks glucose uptake by erythrocytes and muscles, causes lesions in the central nervous systems and influences bioelectric phenomena by altering trans-membrane potentials and by blocking nervous conduction.[101,104]

It has recently been found that mercury binds to the membrane structure in cells and reduces the cell's amount of RNA.[105] This binding disturbs cell metabolism such that cells become fragmented and die. This loss of

sensory input cells causes some of the neurological symptoms of mercury poisoning. Some types of sensory cells, such as the nerve cells of the dorsal root ganglia, were more adversely affected than others. Effect on motor cells of the spinal cord was minimal. Cells of the cerebellum, like dorsal root ganglia cells, suffered loss of RNA.

Mercury compounds vary in their lipid solubility and their diffusibility through pores in cell membranes.[103] Methylmercury is very lipid soluble, a property which is probably responsible for its rapid distribution to all body tissues. Larger mercurials may not be as lipid soluble or as readily diffusible. Even if it is small, the bivalence of inorganic mercury may restrict its diffusibility. Metallic mercury is lipid soluble. Hughes believes that once absorbed by the blood, it exists transiently as the metal dissolved in blood lipids. Once transported to sensitive tissues such as the brain, it is oxidized and fixed within the cells. In the mercuric state it cannot escape the cell because of its bivalency, and therefore, accumulation is possible, producing chronic effects.[103]

In vitro studies have shown that the lethal dose of phenyl and alkyl compounds are one tenth that of inorganic compounds, suggesting easier incorporation of organic compounds because of their organic groups.[106] Similar cytological changes were induced by all compounds but the degree of change differed.[61,66,67,107] In animal experiments, the toxicity of phenyl compounds was comparable to that of inorganic mercury. The discrepancy observed between the results of in vitro and in vivo experiments may be due to the fact that, in vivo, phenyl mercurials are changed to inorganic compounds.

Carcinogenicity: Methylmercury has been found to interfere with liver detoxification mechanisms and this results in the accumulation of N-oxygenated metabolites which may be proximal carcinogenic metabolites of aromatic amines.[108] Because of this, the eventual transformation of hepatic cells to malignant tumor cells may be possible.[109] Metallic mercury may also be carcinogenic or enhance the effect of other carcinogens.[110]

Effect of Mercury on Gametes and the Fetus: Conclusive scientific evidence concerning the effect of mercury compounds on gametes and fetus is lacking. Available evidence indicates that alkyl mercurials are the compounds identifiable with fetal effects. The toxic action of such compounds appears to be directly on the developing fetus or possibly by damage to chromosomes before fertilization of the gametes.[111] Alkyl mercurials more readily cross the placental barrier than elemental mercury and much more readily than inorganic or aryl mercurials, resulting in their greater concentration in fetal tissues and in their capacity for causing fetal damage.[59,60,64]

The only indication of teratogenicity due to alkyl mercurials has been in animal experiments. No such evidence exists for humans. Administration of various alkyl mercury compounds by various routes to pregnant animals has resulted in the following effects on the offspring: cleft palates, reduced birth weight, increased incidence of resorbed litters, changes in the cerebellum and cerebral cortex and consequent postnatal neurological disorders.[111-116]

The occurence of the epidemic of methylmercury poisoning in Minimata, Japan, has provided some information on the effects of this compound on the newborn child. An increased incidence of cerebral palsy was observed

between 1953 and 1959. It has been suggested that this increased incidence in Minimata, together with tissue analyses from affected offspring, and the evidence from histopathological examination of two autopsied congenital cases which revealed brain lesions similar to those observed in adult poisoning cases, indicate alkyl mercurials to be the most probable causative agent.[117] In only one case did a mother of an infant also suffer the effects of poisoning.[118] This suggests that the fetus serves to protect the mother from poisoning in some way perhaps by concentrating mercury and reducing maternal exposure. No such findings were noted in a similar epidemic in Niigata, Japan in 1964-1965.

A few studies to determine the genetic effects of mercury have been conducted.[119] It has been found that methyl, phenyl, and methoxyethyl mercury compounds and the fungicide Panogen (contains methyl mercury dicyandiamide) caused c-mitosis (abbreviation for colchicine mitosis; the characteristic appearance of chromosomes which have contracted more than is usual for mitotic metaphase and lie scattered within the nucleus) in Allium cepa. No other c-mitotic substance is known to effect the spindle apparatus at the low concentrations administered. Polyploidy or aneuploidy resulted from the c-mitosis. All compounds caused tumorous growths. Phenyl and, to a small extent, methyl mercury caused chromosome fragmentation. The author suggested that the compounds tested affect the sulfhydryl - disulfide protein cycle which is involved in formation of the mitotic apparatus.

In an experiment to determine the effect of mercury compounds on the gametes of Drosophila melanogaster,[120] treatment of females with methyl and phenyl compounds resulted in a significant increase in XXY exceptional

daughters but no change in XO exceptions. Males were unaffected. Wings were outstretched and bent.

A few studies relating the effect of alkyl mercury to human chromosomal aberrations have also been conducted. A comparison of the lymphocytes of 9 humans who had consumed methylmercury with those of 4 unexposed controls revealed no significant difference in the chromosome breaks between control and exposed groups.[121] The difference in red blood cell mercury levels between control and exposed groups approached statistical significance. A significant rank correlation was noted between the frequency of cells with chromosome breaks and mercury concentrations.

An in vitro study[122] in which leukocytes from peripheral blood of healthy donors were treated with solutions of methylmercury chloride or methoxyethyl mercury chloride, showed that at high concentrations almost all mitoses exhibited strong toxic or lethal effects in the cells. In the next lower concentration zone, c-mitosis predominated. Signs of chromosome breakage occurred but always in very low frequency.

Pathological Effects of Mercury Vapor and Inorganic Mercury Poisoning: Damage to the lungs has been observed following acute exposure to mercury vapor. Pulmonary edema, erosive bronchitis and bronchiolitis, with severe interstitial pneumonitis and hypoxemia have been reported.[123,124,125]

The kidney, the organ in which the highest concentration of mercury has been found in many animal and human studies, is subject to damage following exposure to mercuric salts which is often from their ingestion. Oliguria (infrequent urination) or complete anuria (urinary suppression) with azotemia (presence of nitrogenous bodies in the blood)

and retention of metabolic waste products in the body has been reported.[126] Necrosis of the proximal tubular epithelium occurs followed by desquamation of the necrotic epithelia. Regeneration of these cells has been observed. Necrosis of cells of the intestinal tract and circulatory collapse may also occur following acute exposure to mercuric salts.[126]

Chronic poisoning is almost always due to occupational inhalation exposure to elemental mercury of a combination of vapor and inorganic dust.[127] Earlier studies conducted when standards of oral hygiene were lower more frequently cite changes in the oral cavity than more recent studies.[128] Mercurialentis, which results from absorption of mercury through the cornea, is considered a symptom of exposure rather than of poisoning.[84] No ocular abnormalities result except for corneal changes. Its incidence is low and its relationship to chronic mercurialism is uncertain. The symptoms of micromercurialism may be associated with functional changes in the vegetative nervous system.[131] Tremors are associated with lesions of the cerebellum and medulla oblongata.[131] Renal effects associated with chronic exposure include proteinuria, nephrosis, which is characterized by massive albuminuria, hypoproteinemia, and edema and nephritis.[82,129-132] Renal lesions have been produced in animals following injection of mercuric salts.[133,134] Mercury accumulates in the cortical and subcortical regions in the collecting tubules, the distal parts of the proximal convoluted tubules and the wide parts of Henle's loop.[135-136]

Pathological Effects of Organic Mercury Poisoning: Organic mercury effects the central nervous system. Autopsy cases of individuals occupationally exposed to fungicidal dusts containing methyl or ethyl mercury have revealed valuable pathological information. The findings of one such case suggested that the common symptom of generalized ataxia was a

result of cerebellar cortical atrophy, selectively involving the granular cell layer of the neo-cerebellum, while the concentric constriction of the visual fields was correlated with bilateral cortical atrophy in the area strata.[137] Another such case revealed engorgement of the vessels of the brain and spinal cord with blood, single swollen structureless ganglian cells with thick dendrites, and necrosis of epithelium in the tubuli of the kidney.[88]

Autopsies on Minimata victims and cats fed fish or shellfish caught in the Bay revealed similar findings.[90] Pathology occurred mainly in the central nervous system. Neuronal disturbances were found in the granular layer of the cerebellum, in the calcarine region, and in the other cerebral cortices. Little or no significant changes were observed in organs other than the nervous system except for an occasional fatty degeneration of the liver and kidney, erosion in the digestive tract, and hypoplasia of the bone marrow.[90]

Symptoms and pathological findings in animals experimentally exposed to methylmercury either by ingestion or inhalation were similar to those of humans.[86] Monkeys appeared to suffer more severe and generalized effects than rats, indicating a possible greater susceptibility of primates to organic mercury poisoning. Not only did the animal suffer degeneration of the cells of certain parts of the brain and spinal cord but kidney damage, siderosis and splenitis were also observed in some animals. One study revealed diffuse injuries to the nerve cells in animals that had not manifested any symptoms after administration.[138] It was suggested that toxic organic poisons cause injury to nerve cells even in very small doses. When the injuries are sufficiently extensive, nerve symptoms arise. This

stresses the potential threat of possible repeated exposures to very small doses of these organic compounds.

Indices of Safe Concentrations of Mercury Compounds: The search for a diagnostic criteria of mercury poisoning has been unsuccessful. On a group basis, there appears to be good correlation between levels of inorganic mercury exposure and levels of urinary excretion.[139] However, in any individual case, there is not likely to be a correlation. There is no clear-cut evidence that workers presumed to have unchanged conditions of exposure will show either an increase or decrease in urinary mercury as duration of exposure increases. Levels of mercury in the urine show little or no correlation with manifestation of poisoning. There appears to be no level above which symptoms can be expected or below which symptoms can be expected or below which symptoms cannot occur.

Most unexposed and some industrially exposed humans have no detectable mercury in blood.[140] Mercury levels in blood tend to parallel the severity of exposure. On a group basis, there is fair correlation between levels of mercury in blood and urine, whereas this is not the case on an individual basis. No evidence has been found that blood levels of mercury rise as duration of exposure increases. Also, no evidence exists of a critical value at which symptoms of poisoning can be expected to occur. Measurable amounts of mercury may persist in the blood and urine for as long as six years after exposure has ended.[141]

Studies have been conducted to determine biochemical changes following exposure to mercury. Analyses to determine levels of glutathione, glucose 6-phosphatese, blood urea nitrogen, delta-aminolevulinic acid (ALA) dehydratase, cholinesterase, coproporphyrin and protein have been

conducted.[142,143,144] Although some changes were observed, no definitive conclusions have been reached concerning their significance. Further research is needed in this area.

A high correlation observed between blood and parotid fluid mercury contents may infer that this readily obtainable salivary secretion may be of diagnostic value as an indirect monitor of blood mercury.[145]

The mercury levels in the blood and hair are two readily accessible indices of exposure to methylmercury.[146] Methylmercury, in contrast to inorganic mercury, rapidly accumulates in the red blood cells and the mercury level in the red blood cells is therefore the best index of the total body burden of methylmercury at any time when equilibrium can be postulated. At equilibrium there is a linear correlation between intake and concentration of methylmercury in each organ or tissue.

Even though methylmercury gives rise to much higher levels of mercury in the hair than in erythrocytes, the use of hair has certain disadvantages.[146]

Although there are large differences in the distribution patterns among different species, the toxic concentration of methylmercury in the brain varies very little among different mammals. In all mammals the lowest level is about 5 to 10ug/g brain tissue. The lowest observed concentration in an autopsied clinical case with neurological signs is 5 ug/g.[147] Sensitivity to methylmercury is more pronounced in the fetal stage of brain development than in any other stage, but research to determine fetal tolerance to methylmercury is lacking.[12,49]

Outbreaks of Mercury Poisoning: Outbreaks of mercury poisoning in different areas of the world have resulted from the alkylmercury contamination of foods. The tragic episodes at Minimata and Niigata, Japan

resulted from the consumption of contaminated fish.[89-93] A New Mexico family was stricken when it fed on contaminated pork.[94,95,96] Incidents resulting from the consumption of bread made with flour which had been prepared with wheat seed treated with an alkylmercury fungicide have occurred in West Pakistan, Guatamala, and Iraq.[97] The most recent and worst incident occurred in February 1972, in Iraq.[98]

Present Standards or Guidelines; Air: The recommended occupational threshold limit value for mercury was lowered in 1971. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended the following threshold limit values (TLV) which are time-weighted average concentrations:[148]

1. Alkylmercurials: 10 ug/m^3 (skin)
2. All other forms of mercury: 50 ug/m^3

In 1968 an international symposium recommended the following "maximum allowable concentration" (MAC) values:[10]

1. Mercury vapor: 50 ug/m^3
2. Inorganic mercury salts, phenyl and methoxyethyl mercury salts: 100 ug/m^3
3. Methyl and ethyl mercury salts. No air concentration is recommended. The mercury level in whole blood should not exceed 10 ug Hg/100 ml (as total mercury). This blood concentration is a ceiling value, and should not be exceeded with continuous 8-hour exposure to 10 ug/m^3 of alkyl mercury in air.
4. Any other mercury compounds not in this list should have separate toxicological evaluation before an MAC value is adopted.

It was also advised that women of child-bearing age should not have exposure to any alkyl mercury compounds occupationally.

The USSR has adopted the following permissible limits;[10]

1. Inorganic Mercury: 10 ug/m^3
2. Alkyl mercury compounds (methyl and ethyl mercury chloride 5 ug/m^3)

The values are to be considered as "ceiling values" which should never be exceeded even for a brief exposure.

The United Kingdom has recommended a safe level of 100 ug/m^3 for mercury vapor, whereas Germany recommends 1 ug/m^3.[149]

No ambient air standard yet exists in the United States. The Federal Environmental Protection Agency recently proposed a national emission standard for mercury which only applies to chlor-alkali plants and primary mercury mines.[4] This emission standard of 5 lbs. per day is based on a desired ambient air level of 1.0 ug/m^3. There are no known state regulations that control specifically the emissions of mercury to the atmosphere or control ambient air levels of mercury. The USSR has established a MAC for metallic mercury of 0.3 ug/m^3 of environmental air for a 24-hour exposure.[150]

Water: In 1970 the U.S. Public Health Service proposes a standard of 5 ppb for mercury in drinking water.[151]

Food: An acceptable (or allowable) daily intake (ADI) has been established for mercury in fish and has been derived in various ways.[34,146] Sweden, Canada, and the U.S. have placed limits on the levels of mercury in fish.[34,152]

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Chapter 4 ATMOSPHERIC ASBESTOS

STANDARD

Exposure to asbestos, a fibrous substance toxic to both man and animal, occurs primarily from air and surface contact. Respiratory illnesses, pulmonary fibrosis, bronchiogenic carcinoma, and cancer of the pleura and peritoneum (mesothelioma) are some of the manifestations of human disability associated with exposure to asbestos. A latent period of 20 to 30 years may exist between exposure to asbestos and development of certain of these cancers.[1] In addition, asbestos is virtually indestructible, resisting heat, alkalies, and acids, and mechanical disintegration merely results in the production of finer fibers which are more likely to be inhaled than larger ones.

In recognition of the hazards of airborne asbestos, the *Environmental Health Resource Center recommends an ambient air quality standard of 1000 asbestos fibers/m^3 based on a 24-hour average sample.* Asbestos fibers include those particles of 5 microns length or greater, which have a length to breadth ratio of 3 to 1 or greater. In addition, since the health effects of short time peak exposures, which may be severe, have not been adequately evaluated, *the Environmental Health Resource Center recommends that a maximum 2-hour average concentration of 1500 asbestos fibers/m^3 not be exceeded more than once in any 24-hour period, more than 30 times per year.*

These standards apply to asbestos defined as any fiber, or any mixture containing fibers, of hydrated silicate mineral including chrysotile, amosite, crocidolite, tremolite, anthophyllite and actinolite. The method of measurement should be that used by the Public Health Service[1a] or equivalent.

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FURTHER RESEARCH

1). Development of techniques for measuring the degree of human exposure to various forms of asbestos.

2). Definition of the role of other contaminants, such as polycyclic hydrocarbons, in the causation of asbestos related diseases.

3). Better quantitative definition of the health effects associated with asbestos exposure.

4). Determination of better sampling and analysis procedures for airborne asbestos fibers, particularly when they exist in conjunction with other forms of particulate matter.

RATIONALE

A variety of studies on workers occupationally exposed to asbestos fibers have shown a higher incidence of cancer of the respiratory system than in the general population.[1,2-6] In addition, significant numbers of mesotheliomas, a cancer of uncertain incidence in the general population, have been found among asbestos workers in factories[4,5] and shipyards.[6] The Environmental Health Resource Center has selected the criterion of mesothelioma as a basis for developing an air quality standard for asbestos.

Most of the information presently available on exposure to asbestos has been collected in industrial environments. As a rule the concentrations in occupational settings greatly exceed those which will affect the general population. Exposure in the work place is non-continuous and for a limited time (40 hours/week) and, to some extent, voluntary. On the other hand, there are many susceptible groups such as infants, the elderly and the infirm who must non-voluntarily endure the urban environment.

Hence, it is necessary to extrapolate occupational exposure data to levels which, on the basis of available knowledge, will not endanger the health of all who may be exposed to a hazardous substance.

Numerous observations of lung specimens have indicated that non-occupational exposure to asbestos fibers does exist.[2,3] For a carcinogenic material, such as asbestos, no level of exposure should be considered toxicologically insignificant to man. The effects of carcinogens on living tissue appear to be irreversible; the tissues do not return to their original condition when the toxin is removed. Hence, a tumor may be initiated and exist in a latent condition for a considerable period of time before it becomes a clinical manifestation. As a result, in man and animals, cancer can develop long after the agent which caused it has disappeared. Exceptions to this principle of zero tolerance should be made only after the most extraordinary justification has been presented including extensive biological and chemical studies and recognition and estimation of the hazard to human health, and only for materials which already unavoidably contaminate the atmosphere. Significantly, the incidence of cancer today may reflect exposures years in the past, and increases in the present level of environmental carcinogens will have a corresponding effect well into the future.

Studies presently available on mesothelioma incidence due to industrial exposure do not report the fiber concentrations to which affected workers were exposed.[4-6] A recent report of the National Institute for Occupational Safety and Health (NIOSH) gives short term fiber concentrations for a number of industrial settings.[1] While these data are of recent origin, and as such are not directly related to the epidemiological studies of

mesothelioma incidence, they do reflect the difference between well and poorly controlled processes; and thus can be used as an estimate of low or severe exposure. Table 1 shows mesothelioma incidence data from several different studies along with high and low concentrations from the NIOSH document for shipyards, textile processes, construction operations and insulation plants.[1] These data are used in Figure 1 to construct a concentration-incidence envelope. The boundaries of the envelope result from extrapolation from the extreme points in the plot using a straight line dose-effect relationship (which seems prudent in lieu of more definitive data). The "optimistic" and "pessimistic" lines reflect mesothelioma incidence at t e most severe and lowest exposure levels; and at the proposed standard of 1000 fibers/m^3 these lines correspond to hypothetical incidences of approximately one in three million and one in five thousand, respectively. The environmental standard represents a compromise between these two extremes and indicates a hypothetical incidence of one in a million that a member of the general population will develop mesothelioma due to exposure to asbestos fibers.

The Environmental Health Resource Center recommends the air quality standard of 1000 fibers/m^3 for asbestos to protect the general and susceptible populations, increase awareness of the hazard, bring about recognition of the sources of exposure and emphasize the need for rigid enforcement of emission standards to achieve this level of air quality.

TABLE 1
INCIDENCE OF MESOTHELIOMA AND
ASBESTOS CONCENTRATIONS IN
OCCUPATIONAL ENVIRONMENTS

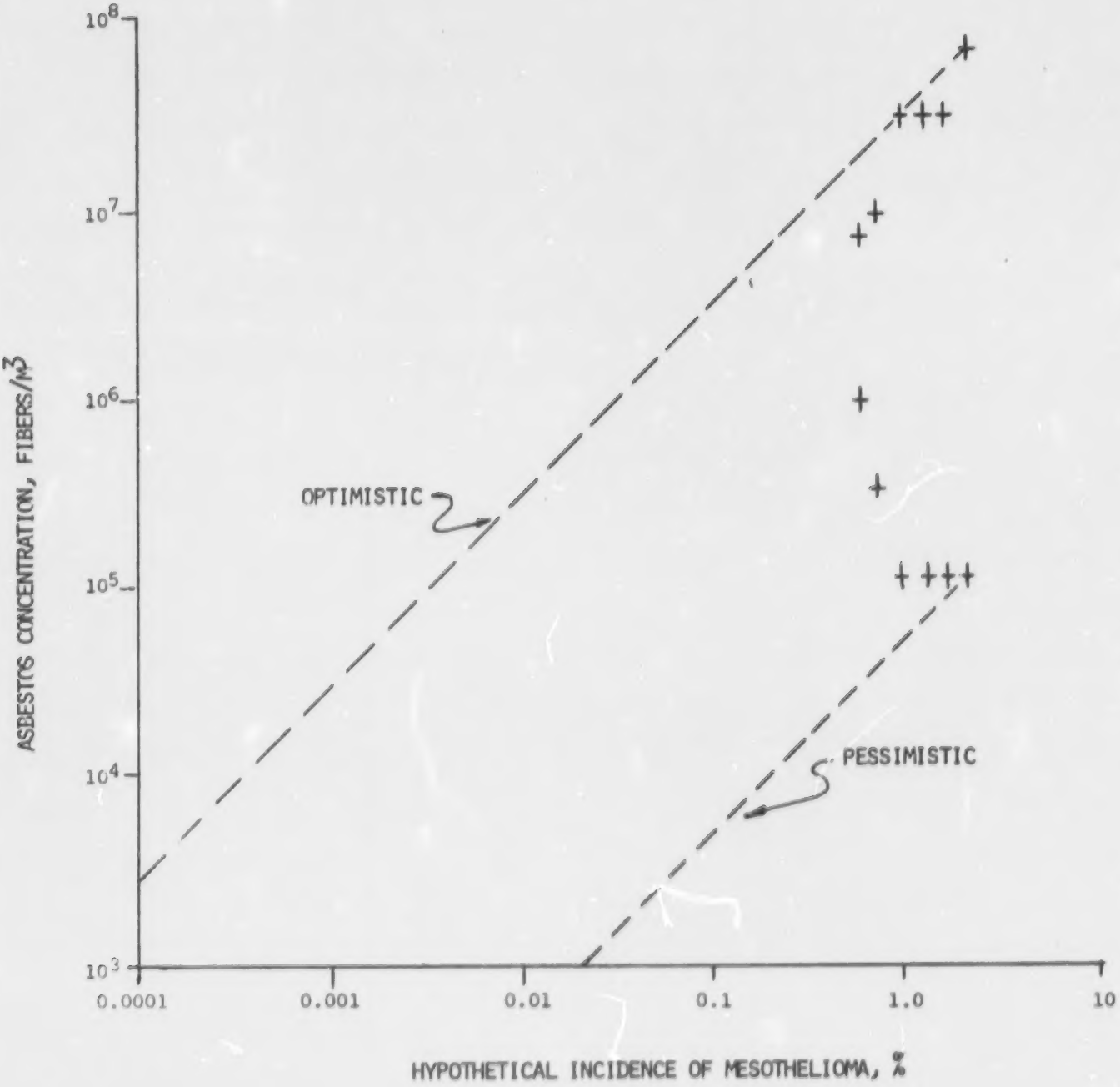
Industry	Cohort Number of Individuals[a]	Mesothelioma Incidence %	Reference	Highest[b] average concentration fibers/cm^3	Lowest[b] average concentration fibers/cm^3
Insulation Plants	689	2.18	65a	74.4	0.1
Shipyards	3000	0.73	6	8.7	0.3
Construction	632	0.63	38	7.1	0.9
Textile Plants	716	1.50	5	29.9	0.1
	1300	1.00	5,66	29.9	0.1
	~1300	1.20	4,22	29.9	0.1

(a) Most of the individuals in these studies had been followed for 20 years or longer.

(b) Concentrations from NIOSH document, Reference 1.

FIGURE 1

EXPECTED LIFETIME INCIDENCE OF MESOTHELIOMA AS A FUNCTION OF EXPOSURE TO ASBESTOS FIBERS*



* Data for plot described in Table 1.

ENVIRONMENTAL ASBESTOS SUMMARY

Introduction: Asbestos is a term referring to a group of fibrous crystalline hydrated silicate minerals. The physical and chemical properties of asbestos, together with its fibrous structure, make it a unique material with a wide range of industrial applications. Its production is increasing rapidly. The world's annual production in 1900 was a few thousand tons, while over 3 million tons were produced in 1968. There are many different types of asbestos minerals. However, only a number are of commercial importance. These are chrysotile, crocidolite, amosite, anthophyllite, actinolite, and tremolite.

The United States utilizes about one-fourth of the world's production of asbestos. Total U.S. production in 1969 was 125,936 tons, which were used in the manufacture of asbestos textiles, paper, and cement products, friction material and gaskets, floor tile, paints, roof coatings, and plastics.[7] The manufacturing process itself and the subsequent use of asbestos-containing material, such as by spraying or sawing, are all potential sources of this hazardous material.

Various chronic human disabilities, primarily involving the structure and function of the respiratory tract, have been associated with the inhalation of asbestos fibers. The manifestations include cough, sputum production, breathelessness (dyspnea), decreased vital capacity and diffusion capacity, pulmonary fibrosis, bronchiogenic carcinoma, and cancer of the pleura and peritoneum (mesothelioma).[1,2,5,8-22] These adverse human health effects have been described primarily in workers occupationally exposed to the asbestos manufacturing process. The documentation of such adverse

health effects has caused a threshold limiting value (TLV) to be set that limits the extent of human inhalation by occupational exposure to airborne asbestos fibers. The TLV is generally related to more acute pulmonary diseases.

Health Effects:

A. Evidence of human occupational exposure to asbestos.

1. Asbestosis. It has been known for over 50 years that occupational exposure to asbestos dust causes asbestosis, a disabling pulmonary disease. The most consistent pathologic change in this disease is a dense fibrosis, containing macrophages with absorbed dust particles, which in many areas obliterate the pulmonary architecture. Elongated bodies, both segmented and unsegmented, can be found in the respiratory bronchioles or embedded in the fibrous tissue. The pleura often shows fibrotic thickening.

Chronic bronchitis and emphysema are often associated with asbestosis. Cor pulmonale is the major complication and the usual cause of death. There is also an increased incidence of carcinoma of the lung in asbestosis.[10,11]

Prevalence of asbestosis among asbestos workers is very high. Selikoff and associates found 339 cases of asbestosis among 392 insulation workers who were exposed to asbestos dust for more than 20 years.[12] In half of these cases, asbestosis was moderate or extensive. In workers with less than 20 years of exposure, radiologic evidence of asbestosis was less frequent, and, when present, much less likely to be extensive. Asbestosis has been produced experimentally in animals.[23-29]

The report on asbestos by the National Institute for Occupational Safety and Health[1] refers to an unpublished paper by William, Baier, and

Thomas (page v-7) who reported 64 cases of asbestosis in asbestos textile plants even when the particle concentration was maintained below 2 MPPCF (two million particles per cubic foot)*. Such data lend significance to the contention by Gee and Bouhuys[30] that more importance should be assigned to controlling exposure to asbestos rather than debating a precise definition of dose-response relationship.

2. Pleural calcifications. Workers exposed to asbestos develop frequent pleural calcifications[31-34]. When multiple or bilateral, these calcifications are regarded by some as almost diagnostic of asbestos related disease. They do not necessarily correlate with asbestosis.

3. Bronchogenic carcinoma. It should be stressed that there are no pathognomonic features of bronchogenic carcinoma associated with asbestos exposure. The first epidemiologic evidence that brochogenic carcinoma might be causally related to asbestos exposure appeared in 1947. Merewether[13] reported 31 cases of carcinoma in 235 asbestos workers who had died with asbestosis between 1924 and 1946. Since then numerous studies have confirmed an association between occupational exposure to asbestos and a higher-than-expected incidence of bronchogenic carcinoma[14,19,35-39 40]. Doll estimated that the risk of dying from lung cancer in asbestos workers is about 10 times greater than in the general male population. Lung cancer from chrysotile has been produced experimentally in animals[41].

4. Mesothelial tumors. A possible causal relationship between asbestos and primary malignant tumors of the pleura and peritoneum (mesotheliomas) was initially considered in the 1960's, after Wagner, et al,[19]

*The relationship of total particles to asbestos fibers is discussed in a subsequent section.

reported 33 cases of pleural mesothelioma in a region of South Africa important for asbestos mining. Since that time, numerous studies suggest a possible causal relationship.[4,5,6,12,38,66] The period between the first exposure to asbestos and the appearance of mesothelioma seems to be quite long, commonly over 30 years.

A serious problem in assessing the incidence of mesothelioma is the diagnosis of this tumor. Strict diagnostic criteria, including an autopsy complete enough to rule out other primary tumors that could metastasize to or involve serous surfaces, are difficult to meet. Mesotheliomas from asbestos have been produced experimentally in animals.[42,43]

5. Impairment of lung function. Characteristic functional changes in asbestosis are the reduction in vital capacity and diffusing capacity. These changes however may precede changes in the chest roentgenogram, or at least occur at a stage when radiographic changes are equivocal.[44-48] The most recent study of Jodoin, et al,[43,49,50] has shown that early effects of asbestos on lung function represent not only restrictive type of impairment (increased static-recoil of the lung, reduction in vital capacity, increased regional inhomogenicities of ventilation, increase in maximal mid-expiratory flow rates), but also obstruction of small airways as evidenced by increased upstream resistance.[51] It was suggested that morphologic changes responsible for increased elastic recoil have intrabronchial and peribronchial rather than alveolar location, resulting, therefore, in small airway obstruction.

B. Evidence of human nonoccupational exposure to asbestos.

1. Fibers in the lung. Fibers coated with a pigmented material found in the lung and sputum of workers exposed to asbestos have been termed

"asbestos bodies". Such bodies, however, have also been found in persons with no known exposure to asbestos. Experiments on animals have indicated that these bodies may result from a nonspecific reaction to any sparingly soluble fibrous foreign body. The term "asbestos body" has been therefore abandoned and such new terms as "ferruginous body" or "mineral-filter-body" have been recommended.[52,53]

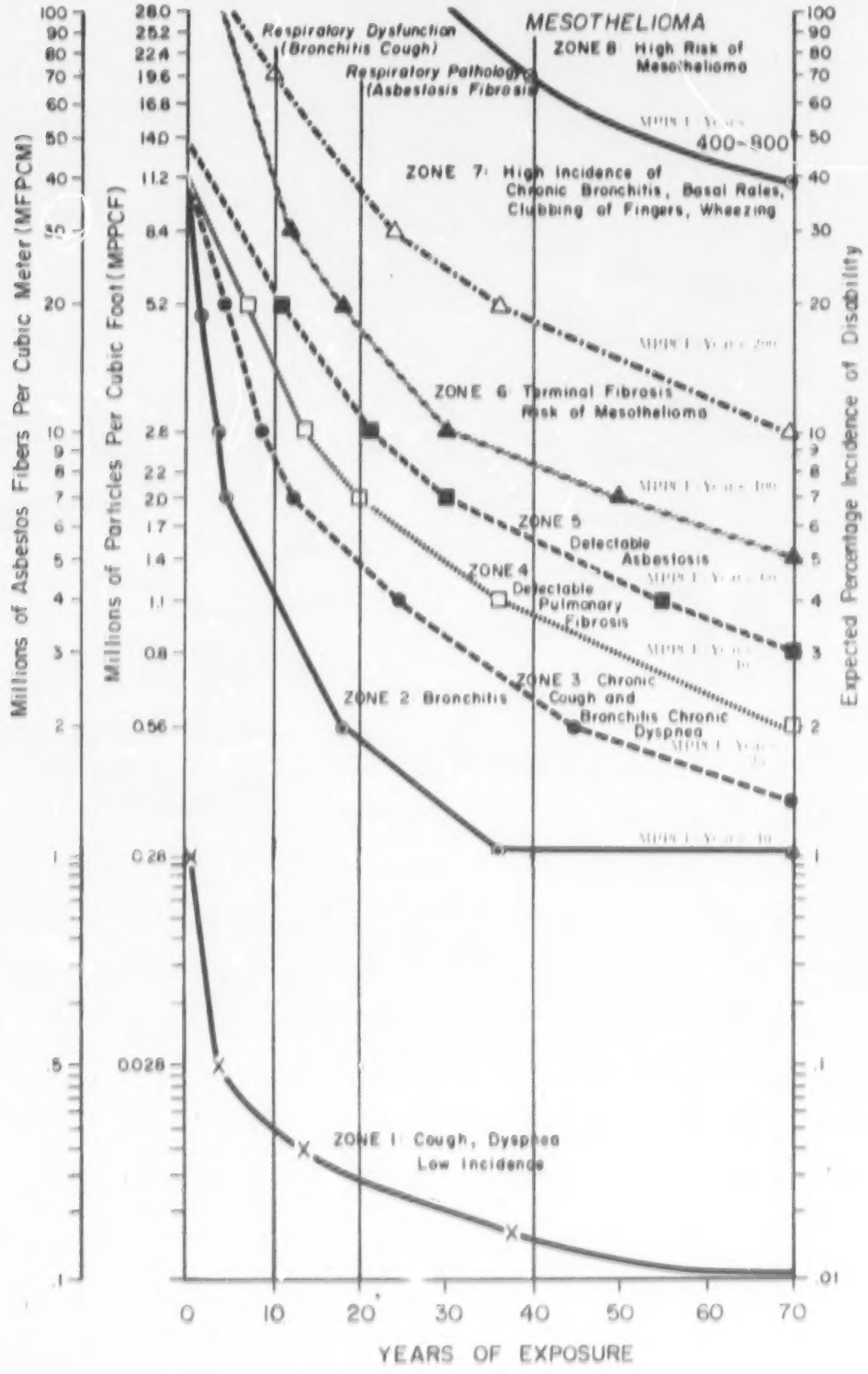
The prevalence of these bodies in random necropsies of urban populations is very high, (Montreal 48%, Pittsburgh 41%, Miami 27.2%, Capetown 26.4% and London 24.3%).[54] Recent studies have been directed not to ferruginous bodies alone, but to the total fiber content of the lungs, whether or not such fibers are coated or uncoated. In a study of 3,000 autopsies in New York City,[55] coated fibers were found in 1,449 lung specimens. In two thirds of these specimens and in one fourth of the specimens in which coated fibers were not demonstrated, thin, uncoated, optically visible fibers were found. In some of these specimens it was possible to demonstrate chrysotile fibers. Evidence is therefore strong that most human lungs contain thousands or millions of fibers, some of which are asbestos minerals; and that exposure is not necessarily related to occupation.

2. Pleural calcifications. Some data from Finland,[56] East Germany[57] and Bulgaria[58] suggest that pleural calcifications might be related to non-occupational asbestos exposure. However, the general opinion is that these calcifications alone may not invariably be considered as an index of asbestos exposure in the general population.

Composite Occupational Exposure Data: Figure 2 displays a composite graphical representation of reported occupational exposure data that relates the degree of risk towards acquiring a particular severity gradation

FIGURE 2 .

OCCUPATIONAL DISABILITY RISK CHART DURING EXPOSURE TO ASBESTOS


Millions of Asbestos Fibers Per Cubic Meter (MFPCM)
Millions of Particles Per Cubic Foot (MPPCF)
Expected Percentage Incidence of Disability
Respiratory Dysfunction (Bronchitis Cough)
Respiratory Pathology (Asbestosis Fibrosis)
MESOTHELIOMA
ZONE 8 High Risk of Mesothelioma
400-800
ZONE 7: High Incidence of Chronic Bronchitis, Basal Rales, Clubbing of Fingers, Wheezing
ZONE 6 Terminal Fibrosis Risk of Mesothelioma
ZONE 5 Detectable Asbestosis
ZONE 4 Detectable Pulmonary Fibrosis
ZONE 3 Chronic Cough and Bronchitis Chronic Dyspnea
ZONE 2 Bronchitis
ZONE 1 Cough, Dyspnea Low Incidence
0.28
0.056
0.0028
0 10 20 30 40 50 60 70
YEARS OF EXPOSURE

of respiratory symptom to the product of particle concentration and years of exposure to that concentration. The data points are based on the concepts presented by Schall[59] and Wells[69], who hypothesize that the product of millions of particles per cubic foot (MPPCF) and the years of exposure determine the severity of respiratory symptoms. As an example, if such a product is 100, the represented zone of symptomology may be the result of 10 MPPCF times 10 years of exposure, or whatever other multiple comprises a 100 curve. Data sources which contribute to the plot are listed in Table 2. The represented curves are slightly different from the British viewpoint[61,62], in that the British Occupational Hygiene Society Subcommittee on Hygiene Standards for Asbestos designated an accumulated exposure of 100 fiber-years/cm^3 as a level that would reduce the risk of contracting asbestosis to less than 1% of those who have a lifetime of occupational exposure to the dust. However, recent review of data relating various diseases to occupational exposure suggests that this standard may well be re-evaluated[65a].

Fiber-Total Particle Relationship: Characterization of airborne asbestos has been a source of some confusion in determining exposure levels. In the past the total particle concentration has been measured using impinger techniques[59]. However, a significant physical characteristic of asbestos particles is their fibrous shape, and animal studies have suggested that longer fibers may be more capable of inducing asbestos related disease[1]. More recently, occupational standards[61] and work place measurements[59] have emphasized measurement of the fiber concentration as opposed to total particle count. Unfortunately, the conversion of data from particles/unit volume of air to fibers/unit volume of air requires information only

TABLE 2

RESPIRATORY DISABILITY AND DEGREE OF

EXPOSURE TO ASBESTOS

(References 2, 16, 17, 18, 63, 64)

MPPCF X YEARS (Dust Index)	HEALTH EFFECT	REFERENCE
Existent ambient	cough: 8% incidence dyspnea: 7% incidence	63
10-100	bronchitis in non-smokers 19% incidence 31% (age 51-65)	16
25	chronic cough: 14% incidence dyspnea: 12% incidence	63
40	detection of pulmonary fibrosis	63
50-60	detection of asbestosis	64
100	incidence of terminal fibrosis	17, 64
200	detection of mesothelioma	2, 18
200	bronchitis, wheezing (46% incidence)	63
400	chronic cough: basal rales; clubbing of fingers; mesothelioma	17
800	highest risk of all forms of respiratory pathology	63

available for certain asbestos sources. The relationship between total particle count and asbestos fiber content in one textile mill may not be the same ratio in another textile mill or another type of asbestos manufacturing process. Ayer, et al,[59] found 12 fibers/cm^3 (12 million fibers/m^3) to be equivalent to 2 MPPCF (2 million particles/ft^3). Twelve fibers/cm^3 represented a significant concentration to McDonald, et al,[60] who assumed that a certain degree of asbestosis may occur at this level, based upon a mathematical assumption that the fiber content of the dust found in an asbestos industry was 10 percent.

As a basis for converting particle counts to fiber counts the Environmental Health Resource Center has selected the data presented by Roach,[62] because of the simultaneous measurement of dust particles and asbestos fibers in this study. The fiber concentration measured in an asbestos disintegration plant was 4 fibers/cm^3 (0.11 MFPCF) for those at least 5 microns long, while the total dust count was 38 particles/cm^3 (1.1 MPPCF). These measurements suggest a ratio of 10% fibers/total dust count. In addition, the following volume conversion factors may be helpful:

$$1\ m^3 = 35.314\ ft^3$$

$$1\ m^3 = 10^6\ cm^3$$

Table 3 shows the relationship between the recommended air quality standard and various threshold limiting values (TLV) for occupational exposure. For purposes of comparison the 10% fiber-particle relationship noted above is superimposed on the ordinate of Fig. 2.

Air Quality Standard Criterion: Although the lower threshold values (TLV) for industrial environments have usually been based upon likely occurrence of asbestosis, the Environmental Health Resource Center has chosen

TABLE 3

ASBESTOS STANDARD AND TLV'S IN DIFFERENT UNITS OF MEASUREMENTS

AIR QUALITY STANDARD OR OCCUPATIONAL THRESHOLD LIMITING VALUE (TLV)[a]	PARTICLES PER CUBIC FOOT (MPPCF)	FIBERS PER CUBIC FOOT (FPCF)	FIBERS PER CUBIC CENTIMETER (FPCC)	FIBERS PER CUBIC METER (FPCM)
5 MPPCF [b]	5 million	500,000	17.66	17.66 million
10 FP cm^3	2.8 million	280,000	10	10 million
5 FP cm^3 (c)	1.4 million	140,000	5	5 million
2 FP cm^3 (d)	560,000	56,000	2	2 million
1 FP cm^3	280,000	28,000	1	1 million
1000 FPCM [e]	280	28	0.001	1000

(a) TLV's based on 8 hour/day, 40 hour/week exposure.

(b) Dressen, et al, Ref. 68, proposed 1946.

(c) ACGIH., Ref. 1, proposed 1970-1971; U.S. Emergency Standard, U.S. Dept. of Labor, Ref. 69, 1971.

(d) Industrial Union Dept. of AFL - CIO (IUD), Ref. 70, proposed 1972.

(e) EHRC recommended standard.

mesothelioma as a standard setting criterion. This manifestation has been selected because the unique properties of asbestos and their contribution to the etiology of mesothelioma constitute a more likely health hazard to the general population than asbestosis. It is well to emphasize that regardless of the criterion selected, any concentration of asbestos fibers above zero represents some degree of risk for any of the respiratory diseases discussed.

Without itemizing all of the epidemiologic data available[1], it is well to point out certain salient features that have contributed to the recommended asbestos standard. These are:

(1) Asbestos fibers in the urban community are a significant contaminant of the air, and constitute an etiological hazard when deposited in the lower lobes of the lung in concentrations that ultimately become a causation of mesothelioma of the pleura or peritoneum[2,3];

(2) The inhalation of a relatively small number of asbestos fibers over a long period may result in a focal concentration at the lung bases[2,3];

(3) Asbestos is practically impossible to destroy and resists heat, alkalies, acids and other means by which materials are usually altered chemically or physically;

(4) The latent period for the development of bronchiogenic carcinoma may be longer than 20 years. The latent period for the development of mesothelioma may be as long as 40 years[4]. There is evidence which suggests that non-occupational exposure to asbestos can take place[2,3,5,19]. Most of the recorded clinical observations do not differentiate between a single or a continuous exposure. This is particularly true

at low levels of exposure, where little difference is observed between those individuals with short and those with long exposure. Investigations of the distribution of mesothelioma in populations occupationally exposed to asbestos indicate a definite correlation between exposure to asbestos fiber and the presence of mesothelioma.[4,5,6,22,38,65a,66]

A number of studies report the incidence of mesothelioma in textile plants,[4,5,22,66] shipyards,[6] and among construction workers,[38] and these are listed in Table 1. Most of the mesotheliomas reported were discovered in individuals who were exposed at least 20 years previously, but none of the studies reports concurrent asbestos fiber concentrations for these time periods. Asbestos fiber concentrations for a variety of process and application areas appear in a recent document of the National Institute for Occupational Safety and Health[1] (NIOSH). These samples have only been collected since 1966, and are of short duration (usually less than an hour). However, the reported high and low concentrations do suggest the difference between well and badly controlled operations; and, as such, may act as an estimate of severe and low exposure. Although it is recognize that these concentrations may not be the same as those which were responsible for mesothelioma, they do serve to outline the range of exposure for industrial workers. Average high and low concentrations, as reported in the NIOSH document, for insulation plants, shipyards, construction operations and textile processes are shown in Table 1.

The plot in Figure 1 displays an asbestos exposure-mesothelioma incidence envelope. The boundaries are based on the extreme high and low

points which appear in the figure. Because low level exposure information is not available, it seems prudent to extrapolate this occupational data to an environmental standard by using a linear dose-effect relationship. This extrapolation is indicated by the dotted lines in Figure 1. The "optimistic" line, based on the assumption that all incidences of mesothelioma resulted from exposure to the highest concentration, corresponds to a hypothetical incidence of approximately one in three million in the general population at the proposed standard of 1000 fibers/m^3. Similarly, the "pessimistic" line corresponds to exposure only at the lowest concentration, and reflects a hypothetical incidence of approximately one in five thousand. The standard itself represents a compromise between these two extremes, and reflects a hypothetical incidence of one in a million that a member of the general population will develop mesothelioma because of exposure to asbestos fibers. The "optimistic" and "pessimistic" bracketing may well be refined by the inclusion of more precise data developed in the future.

The position of the Environmental Health Resource Center is one of encouraging stringent control of asbestos fiber released into the occupational environment or the atmosphere external to the vicinity of asbestos manufacture. Building demolition in particular should be well monitored and controlled. The use of burlap sacks, which have contained asbestos, for wrapping bushes and other plants should be strongly discouraged. The modes of spraying asbestos fireproofing material, and the indiscriminate use of talcum powder on infants should all be evaluated in terms of a potential mesothelioma hazard.

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